Amendments to the specification (clarification on the part of the RCE amendment not being underlined): begins on Page 108.

Summary and Conclusions begin on Page 109.

The previous replies to the 1st OA and 2nd OA (RCE) is maintained, and is incorporated explicitly herein for reference, (to avoid unnecessary repetition). It is respectfully submitted that the PTO's response to our replies to the 1st OA and 2nd OA (RCE) was often generalized, leaving out important parts unanswered, and disregarding important facts (like the secondary factors, our theory and reasons for how our methods would work) or many explanations.

The length of this and the prior reply was necessitated by a) because the examiners are not clinicians and the PTO's thinking pattern in all tree actions deviated so much from the standard of care, and b) because the PTO has repeated itself, and c) because the PTO has presented an unconvincing line of reasoning on a number of occasions (even with their tenets not being substantiated by facts), and d) because the PTO disregarded relevant parts from the prior replies to the OAs or from to prior submitted applications.

Applicant also includes **enclosures**, and **attachments** (copies of selected – relevant – professional publications

Transmittal Form, Information disclosure form (for literature– with enclosed copies), **request of three months extension of time, check** for payment are accompanying this letter. (The IACtr/PTO [ref# 1-116429278 on 4-28-08] has assisted the applicant to calculate fees and what forms to use).

In addition, please note that the **Applicant has lost his attorney representation, is relying on your guidance**, and that his best (timely) contact is through his cell phone **(724)840-0464** –(his mail may not be promptly accessible, if he does not know when it is coming).

Help request from the PTO examiner and Questions:

I would like to continue request help from the PTO including and as needed for claim-drafting assistance **under MPEP 707.07(j)** – (see also #14 at page 35). I'd like to do that not only in general, (as hopefully most of my claims would be in order), but **also** with special emphasis on checking the following:

1) The "**or**" is used in many of the claims, and I would like to be sure that it is not invalidating the claims. E.g.: "said treatment is given at a time selected from the group consisting of, as initial treatment **or** as soon as possible, **or** upon presentation to a physician **or** a health care provider". (Also I would like to be sure that the "given at a time" is clear and acceptable).

2) **Dash ("/")** had been used in some of the original and current claims: in Claim 1-3, 11, for example: (...combined action **SSRI/SNRI, serotonin-2 antagonist/reuptake** inhibitors, ...**serotonin/norepinephrine/dopamine** reuptake inhibition, ... **substance P antagonists/ neurokinin-1** receptor antagonists,...
3) I have noted that even when I had an attorney (and the claims were seen by PTO) many places the word "said" was missing or "the" was used instead [like antidepressant, instead of "said" antidepressant. That created misunderstanding in the case of "substantially of all of said patients". I have corrected these omissions, but at times I also changed the "the" to a "said"; and I would like to be sure that this is acceptable.
4) I'd like to ask you to make sure that no claims contain "means plus function" – as I read that this would not be permissible.

List of referenced / enclosed articles:

Azhar MZ Comparison of fluvoxamine alone, fluvoxamine and cognitive psychotherapy and psychotherapy alone in the treatment of panic disorder in Kelantan – implications for management by family doctors. Med J Malaysia 2000 55(4)402-8.

Barlow DH Anxiety and its disorders (learned alarms) pages 220-225, Guilford Press,1988

Brody A. et al Regional brain metabolic changes in patients with major depression treated with either paroxetine or Interpersonal therapy. Arch Gen Psychiatry 2001; 58:631-640.

Cremers TI, et al Is the beneficial antidepressant effect of coadministration of pindolol really due to somatodendritic autoreceptor antagonism? Biol Psychiatry 2001 Jul 1; 50(1):13-21.

Current Patents 15 Nov 2002 week 0246 at http://scientific.thompson.com/media/cdjournals/gazettenews/202/CPG_News_0246.pfd - enclosed.].

DeRubeis RJ et al Cognitive therapy vs Medications in the treatment of moderate to severe depression Arch Gen Psychiatry 2005; 62:409-416.

Ferris RM et al Buproprion: a new antidepressant drug, the mechanism of action of which is not associated with downregulation of postsynaptic β-adrenergic, serotonergic (5-HT2), α2-adrenergic, imipramine and dopaminergic receptors in brain. Neuropharmacology 22 No 11, 1257-1267, 1983.

Goldapple K. et al Modulation of cortical-limbic pathways in major depression. Arch. Gen Psychiatry, Vol 61, Jan 2004, pages 34-41,

Kramer MS et al The effects of a selective D4 dopamine receptor antagonist (L-745,870) in acutely psychotic inpatients with schizophrenia. Arch Gen Psychiatry 1997; 54:567-572.

Kuoppamaki M et al Differential regulation of rat 5-HT2A and 5-HT2C receptors after chronic treatment with clozapine, chrorpromazine and three putative atypical antipsychotic drugs. Neuropsychopharmacology 13:139-150, 1995.

Landen M. et al A randomized, double-blind, placebo-controlled trial of buspirone in combination with an SSRI in patients with treatment-refractory depression. J. Clin Psychiatry 1998; 59:664-668.

Paton, C. Generic clozapine: outcomes after switching formulations. British Journal of Psychiatry 2006. 189 184-185

Perez V et al A double-bind, randomized, placebo-controlled trial of pindolol augmentation in depressive patients resistant to serotonin reuptake inhibitors. Arch Gen Psychiatry. 1999; 56(4):375-379.

Roth BL et al Chronic mianserine treatment decreases 5-HT2 receptor binding without altering 5-HT2 receptor mRNA levels. European Journal of Pharmacology – Molecular Pharmacology Section, 207 (1991) 169-172

Sharp DM et al Global measures of outcome in controlled comparison of pharmacological and psychological treatment of panic disorder and agoraphobia in primary care. Br J Gen Pract 1997 47(416) 150-5.

Simon NM et al (Longitudinal outcome with pharmacotherapy in a naturalistic study of panic disorder. Journal of Affective Disorders 69 (2002) 201-208.

Spilberger CD: State-trait anxiety inventory. Stanford, Consulting Psychologists' Press 1968, [and reference for it's use in research: Freedman, R at al Psychosomatic Medicine 52:624-630 (1990). – referenced, but reference not included as it is not directly relevant or not so much relevant. (the point was made without the need to enclose the reference).

Stoner, S.C. et al A program to convert patients from Trade-name to generic clozapine Pharmacotherapy 2003; 23(6):806-810 [particularly page 806 second column 3rd line from the bottom on patent expiration

Toth M et al Antagoist-mediated downregulation of 5-hydroxytryptamine type 2 receptor gene expression: Modulation of transcription. Molecular pharmacology 45:1095-1100, 1994.

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- The following copies of enclosures that that were sent with the RCE are specifically incorporated herein due to their importance: (for the actual copies please see the enclosure of the RCE):

1a) Secondary factors in determining unobviousness. From Patent attorney David Pressman, Book: "Patent it yourself". Nolo, 2004 10th edition, pages 5/19- 5/22.

1b) General arguments against obviousness. From Patent attorney David Pressman, Book: "Patent it yourself". Nolo, 2004 10th edition, pages 13/25-13/16.

1c) A14 A request for claim-drafting assistance under MPEP 707.07(j) ... (Showing that the PTO has to give assistance in claim drafting – which is against the PTO statement in the interview. From Patent attorney David Pressman, Book: "Patent it yourself". Nolo, 2004 10th edition, pages 13/46.

Reply to 2nd office action:

In this **line by line/section by section** reply to the 3rd office action (1st after the RCE), for better organization, we put our reply in a tables. Indented to the left or left column is the copy of the 3rd office action's pertinent part, indented to right or right column is or our reply.

From page 5 of OA

The following grounds of rejection of record in the previous office action are maintained:

Claim Rejections. 35 *USC* § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the
> art to which it pertains. or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9,11-12,37,38,41-43,48-50,53-71,95-103, and 126 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating depression, cognitive distortions, smoking cessation, or nicotine withdrawal comprising administering certain antidepressants defined in the specification and prior art, does not reasonably provide enablement for such a method involving any antidepressant whatsoever. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands,* 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman, 230* USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed invention is a method of treating depression and other disorders by administering a drug or a combination of two drugs. It is claimed that the antipsychotic drug improves the therapeutic outcome even in patients not suffering from psychotic symptoms.

The state of the prior art: Combination therapy with antidepressants and atypical antipsychotic drugs has been taught in the prior art. Although a number of drug combinations have been tested and found to be useful, particularly combinations of a serotonin reuptake inhibitor with an atypical antipsychotic, many drugs of both types have not been tested. In particular, typical antipsychotics and dopamine system stabilizers such as aripiprazole have not been tested in the claimed methods. More generally, the full limits of the class of compounds known as "antidepressants" in the language of-instant claim 1 have not been determined, and it is likely that there exist novel compounds with antidepressant activity that have not yet been discovered.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: In the absence of any general theory explaining the action of atypical antipsychotic drugs to enhance therapeutic outcomes with antidepressants, it is not possible to predict the efficacy of any particular antipsychotic for this purpose absent experimental data. Because so many different compounds are known as antidepressants no one example of group of related examples can be predictive for demonstrating the effectiveness of antidepressants combined with antipsychotics generally. Thus the effectiveness of a particular combination therapy of an antidepressant and an antipsychotic for the treatment of depression, cognitive distortions, smoking cessation, or nicotine withdrawal is unpredictable.

The Breadth of the claims: The claimed invention encompasses combination therapies of any "newer" antidepressant with an antipsychotic. The newer antidepressants are defined only in the negative, as not being a tricyclic or tetracyclic antidepressant or a permanent inhibitor of monoamine oxidase. In particular, a vast number of different possible modes of action for an antidepressant are recited in instant claim 12.

The amount of direction or guidance presented: Two hypothetical cases are given in order to illustrate possible uses of the claimed therapeutic method. (p. 16-17)

The presence or absence of working examples: No working examples of the claimed therapeutic methods is provided by Applicant.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as antidepressant/antipsychotic combination therapy. See MPEP 2164.

The quantity of experimentation necessary: In order to practice the claimed invention, one skilled in the art would be required to determine the extent of antidepressants useful in said methods. Because Applicant has provided no working examples, and because the state of the art is unpredictable, many different antidepressants would need to be tested in order to provide a comprehensive understanding of which combinations are or are not useful in the claimed method. Because there is no structural limitation to the full scope of "newer antidepressants" one skilled in the art would have to discover each and every possible compound with antidepressant activity. Doing so would require the synthesis and testing of an enormous number of compounds. In the process of synthesizing the compounds to be tested, many novel and unpredictable synthetic methods would have to be developed. These experiments would be repeated many times in animal models of depression, cognitive distortions, and nicotine addiction, in order to establish their suitability as therapeutic methods. It should be noted that evaluating psychological disorders such as depression and cognitive distortions in animals is more difficult than evaluating a therapy for a nonpsychological condition such as cancer or arthritis. Animal experiments include, along with the actual administration of the potential pharmaceutical compound and collection and analysis of data, additional burdens associated with compliance with animal welfare regulations, care, feeding, and other maintenance of the animals, dissection of dead animals to collect data, and disposal of dead animals after the protocol is finished. Because of the unpredictability of the art and the lack of any generalized method for predicting the pharmacological properties of any arbitrarily chosen molecule, these animal experiments would need to be repeated many times, and involve the maintenance, killing, and disposal of many experimental animals, to establish the suitability or lack thereof for each compound found to possess the desired activity in vitro.

The scale of synthesis, in vitro, and in vivo testing described in the preceding paragraphs would present an undue amount of unpredictable experimentation to require of anyone wishing to practice the invention.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that mayor may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the unpredictability of the art and the lack of guidance or working examples, Applicants fail to provide information sufficient to practice the claimed invention with every possible antidepressant.

Response to Argument: Applicant's arguments, submitted August 27,2007, with respect

to the above ground of rejection, have been fully considered and not found to be persuasive to remove the rejection. Note that Applicant's arguments with respect to the terms "typical antipsychotic," "atypical antipsychotic," "and dopamine system stabilizer," are found to be persuasive and the rejected claims are not rejected for lacking enablement for the claimed classes of antipsychotics. The above rejection is maintained as applied to the term, "newer antidepressant." Applicant argues that this definition of a newer antidepressant is sufficiently well-defined to limit the claimed invention to an enabled class of compounds. However, the definition is still open-ended and not drawn to a class of compounds whose synthesis and use is enabled by the specification and/or the prior art.

Applicant further argues that functional language was allowed in European patent application EP 0966967. This is not relevant to the present prosecution as each patent application is prosecuted on its own merits, and furthermore US patent applications, prosecuted by the US Patent and Trademark Office, are not prosecuted using the same rules as those used by the European Patent Office.

Furthermore, Applicant argues that the allowability of customary English words such as "chair" or "table" in patent claims indicates that customary terms in the medical art such as "antidepressant" can also be used. However, the complexity of the chemical and pharmaceutical art raises the bar for enablement, and claims covering novel, undiscovered pharmaceutical entities are more difficult to enable than novel types of furniture. Inventing a new table or chair does not carry the burden of unpredictable experimentation that is associated with inventing a new drug. Therefore the term "antidepressant" or "newer antidepressant" is not seen to be enabled.

For these reasons the rejection is deemed proper and maintained.

#I of third reply (first reply after RCE):
Re: Claim Rejections. 35 *USC* § 112 does not reasonably provide enablement for such a method involving any antidepressant.

My reply:
We will overcome this objection by amending claims 1-3. (However, it was also asked from the PTO to review and comment of these proposed alternative claims in the RCE pages 40-42). We would also add new claims 131-143 in part to comply with overcoming the PTO's objection.

The following **also** needs to be noted as an active part of our reply:

Note 1) The PTO failed to make a note on alternate claims proposed, (RCE pages 40-42) with the note in the RCE requesting that and noting regulation for the PTO needing to help applicant without attorney representation. (e.g. RCE page 3, 35-36).
Note 2) PTO also failed to allow interview specifically promised, but not granted. (RCE pages 36, 130,)
Note 3) We feel that PTO owes more explanation on how Eu patent application allows issuing a patent as there are treaties between the various patent offices, such as priority date from Eu application, that is also applicable to the US patents. Therefore brushing our answer off with generalized statement that it is not relevant, or that each patent is evaluated on its own merit, therefore not going into a synonymous, and very much analogous explanation on the language allowed at Eu patent application is not acceptable or proper for ground of rejection.
Note 4)Our prior arguments in this regard presented in reply 1 and in RCE are maintained.

From page 11
Claim 65 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's amendment submitted January 8, 2007 with respect to claim 65 has been fully considered and but is deemed to insert **new mater** into the claims since the specification as originally filed does not provide support for the active metabolite of risperidone. As the instant specification as filed contains no description of said metabolite or a method of using it as a therapeutic agent, the specification as originally filed does not provide support for the subject

matter of instant claim 65. See *in re Smith,* 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972).

Response to Argument: Applicant's arguments, submitted August 27, 2007, with respect to the above ground of rejection, have been fully considered and not found to be persuasive to remove the rejection. Applicant argues that administering the metabolite of a drug is a logical and inherent step involved in administering the drug itself, as described fir the case of grape juice being an inherent product consumed when eating grapes. However, even in the case of grapes and grape juice, it is well recognized that fruit juices are not nutritionally equivalent to whole fruit, which contains components such as skin and pulp that provides additional nutritional value beyond what is obtained from merely drinking the juice. Furthermore, the sensory qualities of fruit juice and fruit differ significantly, and the juice is less effective at producing satiety than the whole fruit.

These examples serve to demonstrate that even in a case as simple as the extraction of juice from fruit, isolation of one particular product from a starting material can lead to significant changes in the function of the product.

Analogously, the biological effects of administering a drug are expected to differ form those of administering a metabolite of that drug. For example, the metabolite might be absorbed at a different rate or not at all. It may possess a more rapid onset of action or be inactivated or eliminated more quickly than the parent compound. There may be more than one active metabolite, each of which affects the subject differently.

For these very reasons, there is a significant interest in prodrugs as novel pharmaceutical entities. If administering a compound were inherently identical to administering its active metabolite, there would be no incentive to spend time and money researching a prodrug

that would be pharmaceutically indistinguishable from the known active metabolite.

Therefore the rejection is deemed proper and maintained.

#II of third reply (first reply after RCE):
My reply:
While we maintain our prior standpoint (that this is an inherent step), the PTO's reply is interesting from several point of view.
As we said earlier, we think that most likely if all of our other claims are accepted by the PTO it would be not worth of pursuing this matter. However, we present the following reply:
#II / 1) As reply to the PTO, in regards to that fruit juices are not nutritionally equivalent, it is notable that as regards to medication effect it is not the calorie that counts, but the chemical effect of the grape in this example. So if we would claim grape having some medicinal effect than certainly grape juice (as grounded with our teeth while eating) would be inherently also having the same effect, just like active metabolite of risperidone would be similarly inherent.
#II / 2) Furthermore the PTO argues on the differences in the sensory qualities of fruit juice and the fruit. The PTO is kindly reminded that gastronomical recipes are not patentable as they are so predictable, so that the PTO's argument in this regard is also not applicable and not convincing.
#II / 3) Furthermore, the PTOs conclusion that the extraction of the juice from the fruit can lead to significant changes of the function of the product was not exemplified with the above PTO's argument, and in fact the opposite is true, that if the grape would be claimed to have a medicinal purpose than the grape juice would be inherent, since it is administered while eating and grinding the grape with our teeth. However, if a new applicant would demonstrate that for example the pulp would contain chemicals with some adverse effect, or a previously unrecognized poisonous substance, and therefore prove that purification is essential than new patent for that process can be granted. That would not diminish the fact of inherency being present. Similarly, the same inherency is applied with active metabolite. This is further exemplified by the fact that the PTO's argument would not hold up on drug-drug, and food-drug interaction, that is if grape juice would have an interaction than grape would have too. Therefore that shows the inherency. The same is true with grapefruit, and grapefruit juice, a case where indeed many examples of food-drug interaction apply. Therefore the PTO did not show a convincing line of reasoning and the rejection should be withdrawn.
#II / 4) The PTO further argues that drug metabolites may show differences and refers to the incentives of the drug companies' research on prodrug, and that incentive being lost otherwise. The PTO is kindly reminded that that incentive would not be lost, and just because a patent is being granted for one invention, if some additional advantage can be shown of a prodrug, new invention can be still granted for that new advantage if it is enabled. Therefore the PTO's reasoning was not convincing.
#II / 5) As regards of the PTO's above argument on the prodrug issue, and the incentives being lost for new invention, it is drawn to attention, that the PTO did not reply to our similar concerns of the loss of incentives with the patentability and rejection of our patent, and also on the arguments we had at several parts in our replies on the claimed double standard the PTO was using with our application. [e.g. reply 1, reply 2(RCE)]. Raising the prodrug argument is interesting from the same

point of view. That is that patents on prodrugs usually show additional inventive steps and some kind of new benefits. That can be for example to cross the brain-blood barrier or showing to have fewer side effects and a better risk/benefit/side effect profile. Now if an invention for a prodrug can be accepted by the PTO due to the inventive step of a different risk/benefit/side effect profile, why did the PTO did not accept or did not understood our arguments on the inventive step of the explanation of the new risk/benefit/side effect analysis in our patent application? You may see again why we are concerned with double standards. (Please also see #III/13 clozapine example where a new risk/benefit analysis played a role in patent extension with a new patent also being filed).

Since the PTO did not gave a convincing line of reasoning the rejection must be withdrawn.

From page 12

Claim Rejections· 35 *USC § 103* The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all **obviousness** rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title. if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 6,10-15, 18,22,26,30,36-38,41-43,48,49,51-63,66,70-74,77, 81,85,89,95-105,109-122,124, and 126-130 are rejected under 35 U.S.C. 103(a) as being obvious over Chappell et al. (US patent application 10/001827, Pub. Number 2002/0094986 A1, of record in previous office action) Chappell et al. discloses a method of treating depression, anxiety, or psychosis in a mammal by administering a combination of an antidepressant, a D4 receptor antagonist, (an antipsychotic) and a pharmaceutically acceptable carrier. (p. 1, left column, paragraph 0002) Note that anxiety is reasonably considered to be a cognitive distortion as it involves unreasonable patterns of thought, namely excessive or irrational worry and exaggeration of problems or threats. Phobias and panic disorders are also considered to be cognitive distortions. General types of antidepressants which can be used are listed in paragraph 0021 and include norepinephrine reuptake inhibitors, serotonin reuptake inhibitors, and monoamine

oxidase inhibitors, among others, as described in instant claims 11-13. Selective serotonin reuptake inhibitors include f1uoxetine, fluvoxamine, paroxetine, and sertaline. (p. 3, paragraph 0025) Norepinephrine reuptake inhibitors which may be used are listed in paragraph 0023 and include clomipramine among others, as in instant claims 14 and 15. Other useful antidepressants are listed in paragraph 0181 on p. 8. The compounds used in this invention may all be administered orally, as described by instant claim 38. (p. 22, paragraphs 0460-0462) Various dopamine D4 receptor antagonists can be used, as listed on pp. 15-21. In particular, p. 20, paragraph 0446 lists olanzapine as a useful D4 receptor antagonist. D4 receptor antagonists can be administered in a preferred dose of about 5 to about 500 mg per day. (p. 22, paragraph 0459) Chappell et al. does **not** explicitly disclose a method of administering the claimed treatments as an initial treatment, as soon as possible, or upon presentation to a physician or other health care provider. Chappell et al. does **not** disclose a method where in the antipsychotic is administered in a dose of 2.5-10 mg olanzapine.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy disclosed by Chappell et al. as an initial therapy and/or to administer it as soon as possible. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Chappell et al. already discloses the treatment to be useful as a treatment for depression generally, and because *it is standard practice in the art to administer a therapy promptly once it is indicated*. One of ordinary skill in the art would reasonably have expected success because choosing a particular therapeutic regimen from among the various options available in the prior art is within the routine and ordinary level of skill in the art. It would also have been obvious to one of ordinary skill in the art at the time of the invention to practice the method of Chappell et al. using a dose of 5-10 mg of olanzapine

per day. One of ordinary skill in the art would have been motivated to use this rang, and would have reasonably expected success in doing so, because the range disclosed by Chappell et al. significantly overlaps with the range of the claimed invention, which is considered to represent Applicant's low dose regimen. When the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. See *In* re *Wertheim,* 541 F.2d 257,191 USPQ 90 (CCPA *1976); In* re *Woodruff,* 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). See MPEP § 2144.05 [R-1].

Thus the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's argument, filed August 27, 2007, as applied to the above rejection, has been fully considered and not found to be persuasive to remove the rejection. Applicant argues that Chappell et al. does not provide sufficient guidance or **enablement** to allow one of ordinary skill in the art to practice a method for treating non-treatment-resistant, non-psychotic depression by administering the claimed combination as initial therapy. However, the art is sufficiently **predictable** as regards known antidepressants and antipsychotic agents, as discussed at length by Applicant in his arguments with respect to the enablement of the claimed invention and the ability of one of ordinary skill in the art to practice **off-label** administration of known antipsychotic agents, that one of ordinary skill in the art **would have been able** to reliably use a known agent for these indication **even without a detailed study** providing exhaustive detail as to the effects in each and every possible indication. One of ordinary skill in the art would have recognized how to practice the claimed invention given the disclosure by Chappell et al. that these pharmaceutical combinations are suitable for the treatment of depression and/or anxiety, including those cases of depression and/or anxiety demonstrating neither psychosis nor treatment resistance. P. 1, paragraphs

0006-0007 of Chappell et al. explicitly recite a list of various types of depression including major depressive disorder. The **test for obviousness** in patent prosecution is not the same as that used in the approval of treatments by the Food and Drug Administration, or that used in deciding **malpractice suits**. *It is not required that the treatment be shown to be equivalent to or better than other available treatment options.* ***All that is required is that it be available as one possible option for consideration*** *by the person of ordinary skill in the art.* **Weighing the risks and benefits** of different therapeutic options **is the job of the person of ordinary skill in the art**. The disclosure of Chappell et al. does indeed place the disclosed subject matter in possession of the public. It is noted that Applicant's own specification provides no actual working examples or experimental studies of the claimed treatment, **but merely suggests** that, given the existence of treatment-resistant depression and the danger of suicide in depressed patients, a skilled practitioner could, weighing the risks and benefits, choose to administer an antipsychotic with an antidepressant as initial therapy in order to reduce the overall risk of suicide. **Applicant's own reasoning would be open to the same charges of malpractice as those alleged for Chappell et al.** This risk-benefit analysis is not something novel or unobvious to one of ordinary skill in the art. **Therefore**, one of ordinary skill in the art would in fact be enabled to practice the claimed method based on Chappell et al.

Applicant further argues that Chappell et al. does not teach all of the claimed steps. The only steps recited in the claims as currently pending involve administering a combination of an antidepressant and an antipsychotic to a patient, wherein the patient suffers from non-treatment-resistant, non-psychotic depression, and the treatment is administered as soon as possible. All of these claim elements are either taught by

Chappell et al., **or obvious to one of ordinary skill in the art. (as is the case for administering treatment as soon as possible**. Therefore it is **unclear which additional steps** applicant has introduced. The intended uses recited in the instant claims, for example inhibiting the development of tolerance toward an antidepressant, providing a neuroprotective effect, avoiding worsening of the depression, resisting suicide, avoiding suicidal ideation, and delaying or resisting relapse, **are inherently present** in any circumstance where the claimed drugs are administered to a patient suffering form depression, as all depressed patients are at elevated risk for suicide, and could suffer relapse after treatment.

Applicant also argues that Chappell et al. does **not** disclose a **low dose** for any of disclosed antipsychotics, and that the recited dose range includes amounts that are much higher than the claimed dose. However, one of ordinary skill in the art would naturally be motivated to use the lowest effective dose within the disclosed dose range, given the dangerous side effects of antipsychotic drugs.

Further, Applicant argues that Chappell et al. discloses merely a broad range of conditions, such as "depression" or "anxiety" rather than the specific indications claimed in the instant claims. This is not the case. Chappell et at. specifically recites specific types of depression and anxiety, for example, major depressive disorder, that fall within the terms "major depressive disorder" and "unipolar depression". Given this disclosure, **it would have been obvious** that the therapy can be applied to cases not demonstrating treatment resistance or psychosis. In fact, nowhere in the Chappell et al. reference is it said that the invention is specifically directed toward treatment-resistant depression. Psychosis is mentioned as an additional, distinct condition that can also be treated, but which does not have to be present when practicing the disclosed invention. It is also **noted that Applicant's disclosure does not direct the**

clinician to not administer the therapy to psychotic or treatment-resistant cases, but rather to administer treatment to everyone without considering psychosis or treatment resistance. This is the same scope of disclosure as Chappell et al.

Therefore the rejection is deemed proper and maintained.

#III of third reply (first reply after RCE):
My reply:

#III / 1) In addition to the reasons we have brought up before in our earlier replies, the Chappell reference cannot render our invention obvious as Chappell is suggesting a combination of dopamine D4 antagonist in combination with an antidepressant for the purposes of their claims. However, in view of Kramer (**Kramer MS et al The effects of selective D4 dopamine receptor antagonist (L-745,870) in acutely psychotic inpatients with schizophrenia Arch Gen Psychiatry 1997; 54:567-572** –copy enclosed) the D4 antagonism does not prove antipsychotic activity as the selective D4 dopamine receptor antagonist in that study was ineffective as an antipsychotic.

Since the Chappell reference is specifically basing the argument of their combination on D4 dopamine receptor antagonist activity, the PTO has failed to show that the aforementioned antipsychotic activity of any and all of the antipsychotic compounds in our invention is effected not by the D2 antagonism but specifically through the D4 dopamine receptor antagonist activity.

PTO has failed to show that such a D4 dopamine receptor antagonist activity would be statistically significant in percentage and in clinical effect to produce the needed antipsychotic effect and be clinically significant. Moreover, as we have mentioned in our specification (and provisional) that studies in depression have a particularly high placebo effect up to about 70 percent, so the PTO has also failed to show that the aforementioned D4 dopamine receptor antagonist activity would be sufficient (in their effect, through that action, in their percentage of their antipsychotic action – if there would be any from that receptor activity) to still provide a clinically significant effect despite of the high placebo effect. (Designing such studies would be possible for example with method similar to the Kapur reference provided in our provisional application).
Therefore the PTO have not shown a convincing line of reasoning for the Chappell reference rendering our invention obvious. Therefore the rejection must be withdrawn.

(In addition the Chappell reference was not enabling, therefore cannot be applied against our invention as prior art with insufficient disclosures. – see also later).

#III / 2a) The PTO said: "Note that *anxiety is reasonably considered to be a cognitive distortion* as it involves unreasonable patterns of thought, namely excessive or irrational worry and exaggeration of problems or threats. Phobias and panic disorders are also considered to be cognitive distortions."

The above is only a statement by PTO without showing any existing reference in the literature that this would be the case. Just because a logical step would work in one way, [that is a theory that cognitive distortions contribute to anxiety (or depression)] that does not indicate that the reverse would also be truth, (and specifically that cognitive distortion would be the sole and only reason to anxiety and that anxiety could be equated to cognitive distortion). The PTO errs with jumping to such conclusions without analyzing the facts, and the PTO is not giving a convincing line of reasoning. (Please see our reference from prior reply on the joke as teaching tool in our medical school of the tree scientist getting drunk on alcohol "on the rock". That however does not mean that one can get drunk from ice.) (RCE page 66 fifth paragraph).
While cognitive distortion can contribute to anxiety, it is not true – and there is no evidence to that – that the contrary would be true, that is as the PTO claims that anxiety would be equivalent to cognitive distortion or "reasonably considered to be a cognitive distortion". Anxiety is a feeling, an emotion, and as it was known prior to our applications; anxiolytic drugs exemplified by benzodiazepines, medications were specifically believed of targeting a different pathways than cognitive distortions. The PTO failed to show any prior art to the contrary. It was only us, and for the first time who enabled – and now with the RCE have been reintroduced into our specification – that how antipsychotics can be and should be used for cognitive distortions.
So that the two – anxiety and cognitive distortions are not interchangeable, and cannot be said to be the same as per prior art.
The PTO's statement would have likely also upset some of my mentor psychiatrists, who were teaching me that in the Nazi area denial was a deadly defense mechanism, and I just cannot see of how the overgeneralization of the PTO saying that "anxiety is reasonably considered to be a cognitive distortion" could stand any grounds in that setting. Why would it be a cognitive distortion to feel anxiety (day to day, week to week...) in a Nazi or dictatorial society when all of the facts shows that you are in danger, or that everything that is precious to you is likely to be taken away including your life and your dignity? In addition in our provisional application (that the PTO should be familiar with) we have specifically referenced the Stanford prison experiment (page 54 last paragraph in the original copy with font size 14 of our provisional of which a copy was enclosed along with the submission of the RCE). That showed that any normal person (to the exposure of such stress) would be prone to developing neuroplasticity changes in the same way that is seen in the referenced mental disorders. In less dramatic example (than the above Nazi or prison environment) that principle is still applicable in any stressful situation, (e.g. if your boss repeatedly and unreasonably is giving you a hard time, if you are discriminated against). So in the light of the above, the PTO did not have a convincing line of reasoning in declaring that anxiety would be equivalent to cognitive distortion or "reasonably considered to be a cognitive distortion". The PTO did not "present a convincing line of reasoning as to why the artisan would have found [our] claimed invention to have been obvious in light of the teachings of the references", **and the rejection needs to be withdrawn.** (Ex part Clapp, 227 U.S.P.Q. 972 (Bd. Pat App. & Inter. 1985)." (Rogers JL The Complete Patent BookSphinx Publishing Napervile, IL 2003 page 219).

#III / 2b) Stress test in Spilberger's test is mainly focusing with questions on anxiety. (See ref.: Spilberger CD: State-trait anxiety inventory. Stanford, Consulting Psychologists' Press 1968, [and reference for it's use in research: Freedman, R at al Psychosomatic Medicine 52:624-630 (1990).]).
Now, if it would be true what the PTO states equaling anxiety with cognitive distortion (or the treatment of anxiety with the treatment of cognitive distortion), than **in view of Spilberger**

reference stress would also be equaled with cognitive distortion (since the PTO equaled that with anxiety). Therefore, if difficult people or a client's boss (e.g. a psychopath boss with personality disorder) would be giving a hard time to our client with ample of stress that would translate according to the PTO (in view of Spilberger reference) that the problem would not be with the boss but simply due to the client's "cognitive distortion". That is inaccurate and shows that the PTO's speculation on equaling anxiety with cognitive distortion (or the treatment of anxiety with the treatment of cognitive distortion) is simply an unconvincing line of reasoning. Therefore the rejection must be withdrawn.

#III / 2c) Please also note in reference to the above phenomena of neuroplasticity and specific changes in the brain, that it is notable that anxiety (or depression) – feelings - elicit a cascade of changes. The examples of anxiety that the PTO is referencing to (like panic), in view of prior art had been conceptualized as the disorder as being due to learned fear of panic, and that "classical" or "Pavlovian" conditioning plays a role in panic disorder. (Page 221 lines 15-19 of Barlow) Moreover learning of fear can occur at the level of the single cell. (Page 221 lines 11-12 of **Barlow DH Anxiety and its disorders Guilford 1988**. – copy pp220-225 enclosed). So the PTO claiming that anxiety would be equivalent to cognitive distortion or "reasonably considered to be a cognitive distortion" cannot be a convincing line of reasoning for these reasons either. Anxiety is a feeling, it leads to changes in the brain including synaptic, molecular changes, it involves changes in neuroplasticity and there are many components and sites where the treatment of anxiety can be attacked. These treatment components (psychotherapy-talking therapy, cognitive therapy-talking therapy, pharmacotherapies cannot be equaled on general grounds, or be considered interchangeable also as for their mechanism of action. The PTO erroneously claims the obviousness of such equality without any prior art reference to substantiate such equivalence in the mechanism of action of these diverse therapy modalities. The PTO did not "present a convincing line of reasoning as to why the artisan would have found [our] claimed invention to have been obvious in light of the teachings of the references", **and the rejection needs to be withdrawn.** (Ex part Clapp, 227 U.S.P.Q. 972 (Bd. Pat App. & Inter. 1985)." (Rogers JL The Complete Patent BookSphinx Publishing Napervile, IL 2003 page 219).

Therefore the PTO was basing its conclusions on false grounds.

#III / 2d) It is also of note that the PTO in its' prior office action had tried a similar logic before equating depression with cognitive distortion, but have accepted our response and withdrew the rejection based on our supportive evidence.

#III / 2e) No medication regimen was known and enabled in the prior art to target cognitive distortions. As stated above it was only us, and for the first time who enabled – and now with the RCE have been reintroduced into our specification – that how antipsychotics can be and should be used for cognitive distortions.

Cognitive therapy, a form of talking therapy was known to specifically target cognitive distortions. It is also known that cognitive therapy seemed to affect recovery with unique directional changes in frontal cortex, cingulated and hypocampus relative to an SSRI antidepressant (that is also approved for the treatment of anxiety), and that it was known that the changes may reflect modality specific

effects with implications for different mechanisms. There seems to be a divergent pattern of the two treatment and the initial hypothesis of the top down and bottom up effects seem to be supported by accumulating research. (**Arch. Gen Psychiatry, Vol 61, Jan 2004, pages 34-41, by K. Goldapple et al .** – copy enclosed: page 34 conclusions last sentence, page 38 first column lines 4-7.) On the other hand and in contrast a different talking therapy in part capitalizing on empathy, the Interpersonal therapy did not show difference in the regional brain metabolic changes, and the changes appeared similar with the two forms of treatment. (**Arch Gen Psychiatry 2001; 58:631-640 by A. Brody et al.**)

Therefore (based from #III/2a to 2e) it is likely, that interventions targeting cognitive distortions have a different target mechanism, and again supports that anxiety (or depression) cannot be equated with cognitive distortion. Therefore the PTO has failed to provide a convincing line of reasoning, and the rejection has to be withdrawn. (Ex part Clapp, 227 U.S.P.Q. 972 (Bd. Pat App. & Inter. 1985)." (Rogers JL The Complete Patent BookSphinx Publishing Napervile, IL 2003 page 219).

#III / 2f) Furthermore there is publication to support that for the treatment of panic anxiety the best improvement was achieved (over antidepressant or fluvoxamine) with the addition of cognitive behavioral therapy (**Sharp DM et al Global measures of outcome in controlled comparison of pharmacological and psychological treatment of panic disorder and agoraphobia in primary care. Br J Gen Pract 1997 47(416) 150-5.** and
Azhar MZ Comparison of fluvoxamine alone, fluvoxamine and cognitive psychotherapy and psychotherapy alone in the treatment of panic disorder in Kelantan – implications for management by family doctors. Med J Malaysia 2000 55(4)402-8.) Therefore if what the PTO suggests for anxiety being equivalent to cognitive distortion (or that if "anxiety is reasonably considered to be a cognitive distortion") would be correct, than it would mean that if you treat the anxiety with SSRIs or antidepressant than that would also treat cognitive distortion. Therefore cognitive therapy specifically capable of addressing and correcting cognitive distortions would have no additional value to the SSRIs (or the antidepressants since the cognitive distortions would have been already eliminated by the SSRIs). As the studies above show this is not the case. Therefore the PTO did not show a convincing line of reasoning in jumping to the above assumption that "anxiety is reasonably considered to be a cognitive distortion". Therefore the rejection must be withdrawn. Now, it is also notable, that any negative study in the same area of research would not negate our conclusions as **DeRubeis RJ et al (Cognitive therapy vs Medications in the treatment of moderate to severe depression Arch Gen Psychiatry 2005; 62:409-416)** showed that the degree of effectiveness of cognitive therapy may depend on the therapist's high level of experience or expertise. Therefore there may be a variability in research sites.

Above #III/2a) -2f) [and in #III/14C)] we have given reasons from several different approach of why anxiety cannot be equivalent with cognitive distortions. Each different approach shown above is sufficiently answering the issue even as a stand alone answer.

#III / 3) The PTO also errs on several other grounds: The PTO correctly states (underlined/highlighted above) that "Chappell et al. does not explicitly disclose a method of administering the claimed treatments as an initial treatment, as soon as possible, or upon presentation to a physician or other health care provider. Chappell et al. does not disclose a method where in the antipsychotic is administered in a dose of 2.5-10 mg olanzapine." However, the PTO

continuing that it had been obvious for the ordinary in the art to administer the therapy disclosed by Chappell as initial treatment is incorrect as we have shown that in our prior replies (RCE pp. 25-28 2nd reply #4; January 17,2007 Amendment pp. 69-72 Reply#25), and by the existence of vast number of secondary factors. (RCE pp 32-34 2nd reply #11); January 17,2007 Amendment pp 93-99 and its enclosures). Note that the PTO did not reply or elaborate on our notes of the secondary factors and to our examples of how the existence of secondary factors are crucial in evaluating obviousness.

#III / 4) The PTO further errs on basing the argument (again) that "it is standard practice in the art to administer a therapy promptly once it is indicated." (part underlined above). The "once indicated" is a crucial part, and we have shown that the risk/benefit analysis being in existence at the time of our invention along with publications teaching against and algorithms giving divergent guidelines, to administer a therapy promptly (that is as initial treatment) was not indicated and was not the standard practice. Therefore to administer the combination therapy or the antipsychotic for our claims as initial therapy was not the standard practice as the PTO erroneously insists.

#III / 5) The PTO errs and incorrectly cites "In re Wertheim, 541 F.2d 257,191 USPQ 90 (CCPA 1976); In re Woodruff, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). See MPEP § 2144.05 [R-1]" as other regulations are also do apply that we have specifically referred to in our reply (that the PTO ignored and did not reply to). (January 17,2007 Amendment p. 71 fourth paragraph lines 3-6). The PTO claims that "When the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. ...Thus the invention taken as a whole is prima facie obvious." It is left out that if the differences in doses are crucial than the above regulation does not apply and new regulation codes take place. (We have referenced the above patent book on the other regulations in our reply, and argued of why the low dose is so crucial, and not obvious, and why it would require an undue experimentation to come up with the low dose range.) (See also January 17,2007 Amendment pp. 7-39).

#III / 6) The PTO does not seem to understand of how off-label administration of medications can be used by the clinicians.
The PTO incorrectly states that "the art is sufficiently predictable as regards known antidepressants and antipsychotic agents" with "the ability of one of ordinary skill in the art to practice off-label administration of known antipsychotic agents" and the PTO also errs that "one of ordinary skill in the art would have been able to reliably use a known agent for these indication..."
We have addressed these issues before, (RCE pp. 21-28, p. 31, and Figures 1-3) but let us briefly revisit them.
First of all off-label medications can only be used if there is some support either in case reports, and/or with enablement through sound logic to use the medication off label for that specific subtype of an illness. For the ordinary in the art it is also a crucial step in that decision (that is in deciding if the off-label use is legally and ethically allowed) to use the known risk/benefit/side effect analysis available at that time.

The PTO did not show us any prior art that was either showing our new risk/benefit/side effect analysis - a new and inventive step - allowing for the use of the pertaining medication or medication combination off-label, nor did the PTO show us that the Chappell reference enabled the use of off-

label medication applications for non-treatment resistant, non-psychotic patients as for initial treatment. Both would have been crucial factors for the PTO to claim "obviousness". In absence of doing so the PTO did not show a convincing line of reasoning.
(For an example that a new risk/benefit/side effect analysis was accepted to be a new and inventive step please see the example of clozapine and our explanation later). [#III/13) below]

As we said a mere statement by Chappell to use his invention for a larger group without enablement is not sufficient disclosure and would not enable the ordinary skilled in the art to use Chappell's method for our claims. The vast number of secondary factors that the PTO disregarded show the same. The PTO's line of logic - as presented repeatedly - does not stand the scrutiny of clinical decision making, therefore it was not and could not be obvious for the skilled in the art to follow the same unconvincing logic (or reasoning) that the PTO claims. There was neither enablement nor a discussion of our new risk/benefits/side effects analysis that would have been enabling for the use of our claims or for the use of off-label application in the Chappell reference or in any other prior art. Without these the Chappell reference is not enabled and not obvious for the purpose of our claims.

Therefore the PTO's statement of "One of ordinary skill in the art would have recognized how to practice the claimed invention given the disclosure by Chappell et al. that these pharmaceutical combinations are suitable for the treatment of depression and/or anxiety, including those cases of depression and/or anxiety demonstrating neither psychosis nor treatment resistance" is incorrect as Chappell did not gave disclosure for those uses, and furthermore there was no logic presented or known at the time of the invention that would have permitted off-label use, initial treatment, for our claims. Again the vast number of secondary factors supports our statement. (See also prior page and RCE pp 32-34 2nd reply #11); January 17,2007 Amendment pp 93-99 and its enclosures).

As cited in our prior reply/RCE (page 17): The PTO has disregarded this and the referenced law that **"the examiner cannot use references as prior art if such references have insufficient disclosures." In re Donohue, 766 F.2d 531 [Fed. Cir.1985]. "A disclosure is non-enabling if it fails to place the subject matter of the claims within the possession of the public..." (page 60 lines 35-42).**

#III / 7) Following, in the response to argument at page 15 the PTO further claims as for the reason for the rejection that "The test for obviousness in patent prosecution is not the same as that used in the approval of treatments by the Food and Drug Administration, or that used in deciding malpractice suits. That may be true, but it is irrelevant as we merely needed to show that **the examiner did not "present a convincing line of reasoning as to why the artisan would have found [our] claimed invention to have been obvious in light of the teachings of the references".** The PTO cannot assume in the PTO's reasoning that the artisan would skip clinical steps and be willing to commit malpractice in order to follow the PTO's unconvincing line of reasoning. We have shown that successfully. (See RCE p. 22 fourth paragraph line 11 and Fig. 1-3). (Again it is evident that the PTO examiners are not clinicians and are unfamiliar with the applicable rules and ethics of the medical practice. A clinician cannot use aspirin and say "lets try it off-label and see if it would work for treating cancer" if there is no risk/benefit/alternative analysis discussed with the patient showing that the treatment would benefit the patient and if there is no good reasoning behind using that medication off-label for that intended purpose. (The field of cancer treatment is an excellent example that you cannot withdraw (known and effective) treatment from patients and use

unsupported off-label experimentation for a drug that has less benefit, or a lower risk/benefit ratio.) Therefore the PTO's argument that "it would have been obvious for the skilled in the art" to try a certain medication or that medication combination "off-label" solely based on that the pertaining components were FDA approved for another indication – is an unconvincing reasoning, and is unsubstantiated. This type of reasoning is especially unconvincing if the PTO would assume that the clinicians would recklessly act on such an unconvincing argument that is without a new risk/benefit/alternative analysis being in place in prior art, and without sufficient enablement (by Chappell or any other prior art) the clinician would have ignored the malpractice laws and would have violated the standard of care to have a go ahead with an off-label experimentation. Off label use with enablement and knowing that it would be benefiting the patient with a new risk/benefit/side effect analysis is different from a reckless off-label use that was not enabled. As we have said, the enablement for a subgroup of a larger group is not always the same (and in our case for initial treatment it is clearly not the same, as the secondary factors also support that argument).
Therefore **the examiner did not "present a convincing line of reasoning as to why the artisan would have found [our] claimed invention to have been obvious in light of the teachings of the references", and the rejection needs to be withdrawn.** (Ex part Clapp, 227 U.S.P.Q. 972 (Bd. Pat App. & Inter. 1985)." (Rogers JL The Complete Patent BookSphinx Publishing Napervile, IL 2003 page 219).
(Please note that we have noted these in our RCE e.g. page 17).
On the other hand we had enabled our method and an off label use with our extensive guidance and with our new risk/benefit analysis (including the use for the benefit of the group).

#III / 8) In the response to argument at page 15 the PTO continues that
"It is not required that the treatment be shown to be equivalent to or better than other available treatment options." The PTO errs with its logic presented, as this is not the deciding factor. We were only obliged to show that at the time of our invention the ordinary skilled in the art was not able to use our invention for the purpose of our claims, as the ordinary in the art – in absence of specific enablement for the pertaining subgroup of patients - would have not stayed within the standards of care in doing so. That is we only had to show that the PTO's line of reasoning was unconvincing and the ordinary skilled in the art could **not** follow the PTO's unconvincing line of reasoning as doing so the skilled in the art would have been committed malpractice. As stated above using our invention "off-label" but without explanation and enablement, would be a reckless act, negligently disregarding required steps in our field and would be considered malpractice. Therefore again **the PTO did not "present a convincing line of reasoning as to why the artisan would have found [our] claimed invention to have been obvious in light of the teachings of the references", and the rejection needs to be withdrawn.** (Ex part Clapp, 227 U.S.P.Q. 972 (Bd. Pat App. & Inter. 1985)." (Rogers JL The Complete Patent BookSphinx Publishing Napervile, IL 2003 page 219).

Note that the Chappell reference was not enabling the use of our method as initial treatment for non-treatment resistant and non-psychotic depression for the reasons discussed above and for the reasons stated in our prior replies.

Please also note that the PTO's statement: "Applicant's own reasoning would be open to the same charges of malpractice as those alleged for Chappell et al." is an unconvincing reasoning as contrary to Chappell we had listed extensive reasons, provided enablement and also provided a new and inventive step of a new risk/benefit/alternative analysis enabling the practitioners to use our

invention. Off-label use of medications is possible if there are sufficient reasons documenting that, and if there is an enablement present for that specific subgroup; and if there is a new risk/benefit/alternative analysis present showing clear benefit for the patient over the possible risks. In that later case there is no malpractice violation present, and there is no duty that was breached. (See also #10) below.)

Please also see the vast amount of secondary factors that we have listed in our prior replies supporting our argument. (RCE pp 32-34 2nd reply #11); January 17,2007 Amendment pp 93-99 and its enclosures).

Please note below the example of clozapine that a new risk/benefit/alternative analysis for a subgroup of patients can and was viewed to be an inventive step. See #III/13 below.

The PTO did not "present a convincing line of reasoning as to why the artisan would have found [our] claimed invention to have been obvious in light of the teachings of the references", and the **rejection needs to be withdrawn**. (Ex part Clapp, 227 U.S.P.Q. 972 (Bd. Pat App. & Inter. 1985)." (Rogers JL The Complete Patent BookSphinx Publishing Napervile, IL 2003 page 219).

#III / 9) At page 15 the PTO continues:
"All that is required is that it be available as one possible option for consideration by the person of ordinary skill in the art." While the PTO's statement may be correct as it stands alone, it is incorrect in the context of the rejection. That is the Chappell reference had **not enabled** initial treatment for non-treatment resistant, non-psychotic depression, **therefore above stated requirement** "that it be available as one possible option for consideration" **was not met**. The Chappell reference was not enabling for the purposes of our claims. Therefore the rejection must be withdrawn.

In addition the PTO had made its unconvincing line of reasoning based on assumptions that were erroneous, and these errors were shown in the prior replies. Therefore the PTO cannot skip these logical steps and continue with unsupported conclusion or basing the old or new reasoning on these unsupported and disregarded steps. (For example that

A) that the Chappell reference was enabled for the use of our claims (incorrect)
   a) that the D4 receptor antagonism has the claimed antipsychotic action **in view of Kramer**, (see #III/1 above),
   b) that the Chappell reference was enabled (including initial treatment, non-psychotic, non-treatment-resistant depression, (incorrect);
   c) that the Chappell reference was enabled for reduction (resisting or "prevention") of suicide, (incorrect);
   d) that the Chappell reference was enabled for reduction (resisting or "prevention") of relapse, (incorrect);
   e) that the Chappell reference was enabled for providing neuroprotective effect, (incorrect);
   f) that the Chappell reference was enabled for the use of substantially all or all patients as initial treatment for the above use, (incorrect);
   g) that the Chappell reference was enabled our claimed uses would be inherent (incorrect); (see also later #III/14)

B) The PTO also cannot disregard the fact that
   a) with the old risk/benefit alternative analysis in place as standard of care at the time of our

invention and
b) with the risks involved of combining multiple medications (for which we even draw attention in our utility)
c) with the strong teaching against of using antipsychotics for non-psychotic, non-treatment resistant depression, (for which again we draw attention at our utility)
d) and with a vast amount of clinical guidelines and algorithms in place guiding clinicians to follow a divergent path, to start the treatment as monotherapy (antidepressant) and only proceed at a much later step (with treatment resistant depression) [for all of these we have made the PTO aware in our prior replies]

The clinician could not have proceeded with our invention without our enablement.
So the PTO cannot disregard all these facts and say that the skilled in the art would have possibly and reasonably skip all these steps violating the standard of care. The definition of violating the standard of care (under which term it is understood a substandard care, harming the patient, not offering more and reasonably expected and explained benefit for the patient). Violating the standard of care also means malpractice. The clinician has to stay within the standard of care, therefore without enablement for the pertaining subgroup of patients could not have used and – as the secondary factors show – did not use the PTO's unconvincing line of reasoning. However, the standard of care may change to the better with new inventions providing enablement such as ours.

The PTO cannot say that the skilled in the art would be skipping these steps or the PTO cannot say that for enablement "all that is required is that it be available as one possible option for consideration by the person of ordinary skill in the art", as if that option cannot be used for a subgroup without enablement it would be not a viable option any more. From the above it is understood that unless a new risk/benefit analysis is also provided giving sufficient guidance for the skilled in the art of why it would be the patient's interest to act on our recommendation and invention, the skilled in the art - in lack of that guidance - could not possibly accept the Chappell reference as "one possible option for consideration". This is so as it could not be an option or consideration if it leads to committing malpractice and violating the standard of care. We have said it before (see RCE p. 22 fourth paragraph line 11 and Fig. 1-3) that the PTO cannot assume that the skilled in the art would commit a malpractice (in lack of enablement for our claims in prior art) just to prove that the PTO's erroneous reasoning is convincing and to provide basis with that unethical and unlawful act for the rejection of our claims. This would be a logical error form the PTO.

The skilled in the art would have had no reason or explanation of why to administer combination therapy or the atypical antipsychotics for initial treatment (for the purpose of our claims) – either from prior art or from the lack of guidance in this regard from the Chappell reference – which therefore is not enabled for the purpose of our claims)

So the deciding factor is not what the PTO claims: "All that is required is that it be available as one possible option for consideration by the person of ordinary skill in the art." While the PTO's statement may be correct as it stands alone, it is incorrect in the context of the rejection.
This is **not** the deciding factor, but to show **if** the PTO had a convincing line of reasoning. If it is unconvincing, that is the **PTO did not "present a convincing line of reasoning as to why the artisan would have found [our] claimed invention to have been obvious in light of the teachings of the references", the rejection needs to be withdrawn.** (Ex part Clapp, 227 U.S.P.Q. 972 (Bd. Pat App. & Inter. 1985)." (Rogers JL The Complete Patent BookSphinx Publishing

Napervile, IL 2003 page 219). That is the deciding factor.

The PTO also disregarded the vast amount of secondary factors – not just the mere passage of time - supporting our argument. (RCE pp 32-34 2nd reply #11); January 17,2007 Amendment pp 93-99 and its enclosures).

The PTO – despite of our explanation – has said in this office action that it was still unclear for them of which additional step we introduced. (We understand that the examiners are not clinicians, but please refer again to RCE and in particular to figures Fig. 1-3).
We have presented a new risk/benefit analysis that makes the use of our claims possible and even necessary [with the exception of the patients' refusal [that we have also discussed in our provisional]. (Please also see our guidance and reasoning for the benefit for the group in the example of appendicitis, and how that same principle should be applied also in psychiatry. We gave guidance for the need of risk/benefit analysis. We have enabled the use of our claims.) With this the initial treatment is be enabled. We will revisit and discuss the new risk benefit analysis as acceptable new step for an invention with the example of clozapine. (#13 below, and #VII/8)

#III / 10) At page 15 the PTO continues:
"Weighing the risks and benefits of different therapeutic options is the job of the person of ordinary skill in the art. The disclosure of Chappell et al. does indeed place the disclosed subject matter in possession of the public." This is an erroneous statement, and **would be only correct if we would disregard the rules of the medical art and my prior statements**. Since the weighting of the risk/benefit/side effect for initial treatment for non-treatment resistant, non-psychotic depression is the job of the person of ordinary skill in the art as the PTO states, that person was not able to use the Chappell's not-enabled disclosure, and was not able to follow the unconvincing line of reasoning by the PTO. Therefore the PTO presented an erroneous logic. That was all that we needed to show in our reply to get the rejection withdrawn. In addition **all what was stated in our answer #III/6)-9) above also applies here.**

The PTO assumes with the above statement that the PTO can continue with the unconvincing line of reasoning that the skilled in the art would have found it obvious to use our invention without guidance or enablement form the prior art and that the skilled in the art would have followed the PTO's unconvincing line of reasoning, please the PTO and violate the standard of care and therefore committing malpractice. This reasoning is unconvincing. The skilled in the art cannot act on something that is not enabled to which there is no sufficient reason given for the benefit of the patient or the benefit of the group of patients. The skilled in the art cannot use off-label medication if there is no sufficient reasoning behind it, if the risk benefit analysis is not shifted significantly toward the benefit (for that subgroup of patients). The skilled in the art cannot disregard the standard of care cannot disregard the clinical guidelines and teaching algorithms if there is **no** good reason behind it to follow a divergent path for the patients' benefit. The skilled in the art cannot ignore a strong teaching against in the prior art and go with an unexplained suggestion from Chappell without enabling (for the purposes of our claims and for the subgroup of our patients). The PTO assuming that the skilled in the art would follow such an unconvincing reasoning is just not true. Secondary factors (and not just passage of time) that we have presented earlier (and what the PTO disregarded) also supports to this fact. (RCE pp 32-34 2nd reply #11); January 17,2007 Amendment pp 93-99 and its enclosures).

Again the PTO did not "present a convincing line of reasoning as to why the artisan would have found [our] claimed invention to have been obvious in light of the teachings of the references", and **the rejection needs to be withdrawn.** (Ex part Clapp, 227 U.S.P.Q. 972 (Bd. Pat App. & Inter. 1985)." (Rogers JL The Complete Patent BookSphinx Publishing Napervile, IL 2003 page 219).

The PTO also did not present any prior art that was enabled for the purpose of our claims, or that would have presented in any similar way to our new line of arguments and to our enablement, or that would have discussed our new step for a new risk/benefit/side effect analysis. None of those have been published before our application. Therefore our invention was novel and unobvious. **Introducing a new risk/benefit analysis which (along with other guidance) enables new methods to save lives at large scale is a surprising new discovery. The secondary factors also support to that fact.** (RCE pp 32-34 2nd reply #11); January 17,2007 Amendment pp 93-99 and its enclosures). (See also #III/13, and #VII/8).

#III / 11) At page 16, the following statement by the PTO is also not substantiated and is incorrect:
"Applicant's own reasoning would be open to the same charges of malpractice as those alleged for Chappell et al." That was in part discussed **under #III/6-10)** above. While anybody can be sued for alleged malpractice, there are laws that decide on the outcome and that on what basis the malpractice claims can be or cannot be substantiated. I have clearly described in my prior replies the facts that are thought in risk management courses: deviating from the standard of care (being substandard), and not going though and not discussing the risk/benefit/side effect analysis is an automatic malpractice. (See RCE p. 22 fourth paragraph line 11 and Fig. 1-3). If you adhere to the guidelines (and we did, as we presented a new and risk/benefit analysis that was substantiated; we draw attention to our new guidance) you do not violate the duty for care, and you do not commit a malpractice. There is a big difference between the two. Even if erroneously sued, explaining to the jury (and judge) our guidance and enablement, the benefit of the group, the new risk/benefit analysis, showing the documentation of discussing the risk/benefit/alternative analysis with the patient would substantiate that we acted properly even if the medication(s) were used'off-label'. Therefore we would **not** be liable and a defense verdict would be returned. The PTO is making an erroneous assumption: "Applicant's own reasoning would be open to the same charges of malpractice as those alleged for Chappell et al." This is simply not the case. Therefore the PTO did not show a convincing line of reasoning.

The PTO makes this unsubstantiated claim that "Applicant's own reasoning would be open to the same charges of malpractice" only by ignoring that I did emphasize the need for going through a risk/benefit/side effect analysis, that I did present new information and guidance of how other factors, the benefit of the group needs to be also considered in the risk benefit analysis in order to save lives, that the benefit of the group is an important factor needed to be taken to consideration, and by ignoring that I was providing an enormous amount of guidance and enablement in my specification (including parts now re-entered to the specification with the RCE). (See also #VII/8, and #III/13)
Therefore the PTO cannot claim that "Applicant's own reasoning would be open to the same charges of malpractice as those alleged for Chappell et al." This is simply not substantiated. (Please also see

#III/9) above.

The PTO than states: "This risk-benefit analysis is not something novel or unobvious to one of ordinary skill in the art. Therefore, one of ordinary skill in the art would in fact be enabled to practice the claimed method based on Chappell et al." This is out of context and therefore incorrect: The risk-benefit-side effect analysis – as a principle - was indeed in existence, and that is why the ordinary skilled in the art was not able to use the PTO's unconvincing line of reasoning. The use of initial treatment for non-treatment resistant and non-psychotic depression was not enabled in prior art in part because of the existing standard of care and existing (old) risk/benefit/side effect analysis that was known to the art, (and that there was a strong teaching against of using antipsychotics for non-psychotic, non-treatment-resistant depression) at the time of our invention. All these standards were known to the art or referenced in our specification or replies (risk of neuroleptics and their combination with antidepressants: utility p. 3, lines 29-32, p. 4, till line 22, teaching against: utility p. 3 lines 3-8; clinical guidelines in existence instructing of taking a divergent path, (e.g. algorithms) : January 17, 2007 Amendment pp. 95-96 and its enclosures). However, with the new risk/benefit/side effect analysis presented by us – a new step – the use of initial treatment for non-treatment resistant and non-psychotic depression was enabled (and that was not enabled previously). (See also Figures 1-3 in RCE for example). Please also see the example of clozapine that a new risk/benefit/alternative analysis for a subgroup of patients can be and has been viewed as an inventive step.) (Please also see III/13, VII/8)

Contrary to the PTO's statement of 'one of ordinary skill in the art would in fact **not** be enabled to practice the claimed method based on Chappell et al', and the above lines of PTO statements are unconvincing as a line of argument, and therefore the rejection should be withdrawn. (Ex part Clapp, 227 U.S.P.Q. 972 (Bd. Pat App. & Inter. 1985)." (Rogers JL The Complete Patent BookSphinx Publishing Napervile, IL 2003 page 219).

The following lines in the current office action at page 16 are just re-phrased prior statements from the PTO and are only mere statements by the PTO without any kind of substantiated support given , or without any convincing line of argument being presented:

#III / 12) At page 16 the PTO states: "All of these claim elements [non-treatment-resistant, non-psychotic depression, as soon as possible] are either taught by Chappell et al., or obvious to one of ordinary skill in the art." (as is the case for administering treatment as soon as possible).
The first part is clearly incorrect as these claim elements specifically are not addressed by Chappell, and equally important **they are not enabled by Chappell**. As regards to the PTO's claim here for obviousness based on that treatments should be administered "as soon as possible" it is also incorrect as the correct statement would be that the **safest** treatments (with best risk/benefit ratio) should be administered as soon as possible and **if** other rules in the medical art are also followed (and as we have discussed these above). The combination therapy, or antipsychotics as in our claims were not considered the safest treatment to be administered as soon as possible for the purpose of our claims, there was a strong teaching against of that method, there were clinical guidelines in place instructing of taking a divergent path, as both the secondary factors (other than the mere passage of time), and our prior arguments extensively revealed this. (RCE pp 32-34 2nd reply #11); January 17,2007 Amendment pp 93-99 and its enclosures). So the PTO's line of reasoning again is unconvincing.

#III / 13) The PTO further states that: "Therefore it is unclear which additional steps applicant has introduced." Figures 1 and 2 compared to Figures 3 in the RCE along with the above written answers; and along with our arguments in our prior replies; and along with the specifications now re-entered with the RCE; clearly indicate that new step; that a new risk/benefit/side effect analysis was described (and enabled in our specification). This is a crucial step in enabling the use of our invention for initial treatment for substantially all or for all patients in our claim. (In part we have already addressed this above e.g. #III/7-12, and #VII/8). Please also see "discussion of new claims" section in this reply where we have highlighted in bold the language used from the specification that was also used in the claims pertaining the risk/benefit analysis.

#III / 13b) Furthermore, prior intellectual property rights as exemplified by Clozaril (clozapine) also indicates that a new risk/benefit/side effect analysis and enabling of such new step is protectable by intellectual property laws that give incentives for such new inventions.
It is of note that neither copyright nor trade secret was applicable to this example, so that the only protection that could have been achieved was by the patent laws. In fact new patents for clozapine were filed that extended its' monopoly for 37 years after the discovery of this drug.
It is also of note that this applicant has lost his attorney representation so the information provided below comes primarily from the literature and Internet search.
It is also of note that any application for a patent of an invention or for a new and inventive step that can provide patent protection – or patent extension (giving a new period) through another/new patent application – is solely the choice of the inventor or intellectual property owner. If for any reasons there would be no new patent application on clozapine filed with the PTO and if the same patent principles would have been applied outside of the PTO's jurisdiction but still relying on the same principles – as a proof of novel unobvious and inventive step – that would not decrease by any way the point we are presenting here, that is, that **a new risk/benefit/side effect analysis as applied to a subgroup of patients can be a new and inventive step**. That new and inventive step indeed has lead to clozapine's intellectual property protection way beyond the original patent's expiration date. (See references below).

#III / 13b-1-a) It is a historical fact that clozapine (Clozaril) was known to have antipsychotic effect long ago before it went to clinical use. Clozapine was developed by Sandoz in 1961.
[see GB980853, and US3539573 not appearing until 1970; and GB1418363 and US3962248, - **Other patents have focused on assessing the patients' suitability for such treatment – indicating that such an assessment and analysis similar to a risk benefit analysis as a step of our claims are patentable** [WO9631621, WO9721833, WO9732037]- see also **Current Patents 15 Nov 2002 week 0246** at
http://scientific.thompson.com/media/cdjournals/gazettenews/202/CPG_News_0246.pfd - enclosed.].
Clozapine was introduced in Europe ten years later, but in 1975 after reports of agranulocytosis and consequent death of some patients it was voluntarily withdrawn by the manufacturer. **It was only when a new risk/benefit/side effect analysis was demonstrated** (the concept similar to our inventive step), - that is in the case of clozapine that overcoming the risk of agranulocytosis with regular monitoring (and not dispensing the medication if the blood work was not done [an

unsuggested modification; a secondary factor]) and by showing that clozapine provided a long felt need unsolved by others for a subgroup of treatment-resistant schizophrenic patients [also a secondary factor, that is *that contrary to prior art teaching the risk of giving that medication was less than the gain achieved – again this is showing a remarkable similarity as for the secondary factors but not for obviousness to our application*], only then it was again used still enjoying intellectual property right protection the patent expiring in 1998. (In the United States it was prescribed since 1989. [see also **Stoner, S.C. et al A program to convert patients from Trade-name to generic clozapine Pharmacotherapy 2003; 23(6):806-810 [particularly page 806 second column 3rd line from the bottom on patent expiration – copy enclosed.** {For an article on the recent introduction of generic clozapine in Europe please refer to: **Paton, C Generic clozapine:outcomes after switching formulations. British Journal of Psychiatry 2006. 189 184-185 /page 185 first column after the summary lines 4-7/**].

#III / 13b-1-b) The above proves our point: a new risk/benefit analysis for a subgroup of patients is an inventive step leading to patentable protection.

It is also of note that despite of similarities in the principles of the inventive steps the principles in the clozapine example also shows **marked differences** to our invention **(to our advantage)**:

A) In case of clozapine the method (of administering the same medication was used even after the inventive step) as earlier clozapine was administered to the whole group of schizophrenic patients that have included (by definition and by chance) an unidentified subgroup of treatment-resistant schizophrenic patients as well. (The patentable discovery in case of clozapine was monopolizing on using a new risk/benefit analysis for that subgroup).
In contrast, in our invention the aforementioned claim uses were never used before! This is a critical difference – an advantage - in allowing the issuing of our application.

B) It is also notable (what the clozapine patent owners could have used (and maybe did use) for argument and still winning) that there was a difference in in the risk/benefit analysis before and after the agranulocytosis and the lethal side effect became known. That is, earlier with the first introduction of clozapine psychotic patients could receive the drug simply because it was effective in treating schizophrenia. However, that old risk/benefit analysis was insufficient later once the agranulocytosis as serious side effect was revealed. Therefore the standard of care was changing and a new (third) risk/benefit analysis was required to overcome the obstacle (the skilled in the art's inability to use the drug). Once that was provided with patient monitoring (regular WBC/platelet count, new regulations on dispensing or no dispensing the drug) and by showing a long felt unsolved need, the method for a new invention was in place also leading to extending the patent life of clozapine for 37 years after it was known to have an antipsychotic action.

The point is that the risk/benefit analysis does change over time and "obviousness" for the skilled in the art was not in place to use clozapine once the agranulocytosis was known (at least not until the new risk/benefit analysis was explained).

That was an essential point that the clozapine patent owners could have argued if the PTO would have attempted "obviousness" objection for re-introducing clozapine and resulting in the patent extension of that drug through new patent applications.

#III / 13b-2) Now if you do the math and if the PTO's unconvincing lines of reasoning would be true (that is the PTO perplexing in its reply of not recognizing a new and inventive step on the risk benefit/ side effect analysis as it is applied to my case or as it was similarly applied to the clozapine; and the PTO stating that my invention – and therefore very similarly the inventive new steps in case of reintroducing clozapine would all be obvious) than how come clozapine enjoyed intellectual property protection with the patent expiring in 1998 (Stoner, S.C. et al Pharmacotherapy 2003; 23(6):806-810 [particularly page 806 second column 3rd line from the bottom on patent expiration – copy enclosed) when the clozapine's antipsychotic effect was known 37 years before, as early as in 1961. No patent term can last in the US for 37 years, unless new invention, a new risk benefit analysis with secondary factors like a long felt need unsolved by others (for a subgroup of patients) is in place (giving a new protected period).

#III / 13b-3a) The parameters of patentability about any new invention can be in place regardless of the intellectual property owners decision to recognize in time to file or not to file a patent application. (Of course if patent application is not filed no patent can be issued, but the invention and the principles for the patentability are still there. Nobody had patent on the Internet yet it was undeniably a new invention). The above clozapine example is no exception. As the PTO knows we are not represented by patent attorneys any more which severely limits our ability to defend our application. So if for any reason – and in contrast to the enclosed Current Patents article - there was no new patent application filed with the PTO (or if another agency stepped in lieu of the PTO on clozapinebut relying on similar patent laws and principles) that would not limit the facts, that in the case of clozapine the new risk/benefit/side effect analysis, and the secondary factors like a long felt need unsolved by others did prove a new inventive step for a subgroup of patients (that was not enabled for the larger general diagnostic group). That effort was honored, and no generic medications (clozapine) was allowed protecting the interest of the inventor for 37 years after the knowledge that clozapine had antipsychotic effect. In addition to the new risk/benefit analysis the new invention as - in the case of clozapine - targeted a subgroup of patients.

#III / 13b-3b) Please be patient for this step even if it seems irrelevant at first. It is very much relevant as an analogy, and analogies and case laws are often used to make a point.
Now the above (in #13) should be understood with other information – analogy - about the law in place: I was taught during my residency training that up till several years ago the prosecuting attorneys were not able to bring doctors to malpractice court who were sleeping with their patients. That was not because the law was any different, but the missing link was not recognized by the attorneys: One of the attorneys argued that the missing step (in the duty to care) was the violation of trust from the doctor to patient, and with that (newly introduced) step in place the breach of duty and the malpractice was proven. In our case; and in the case of clozapine the new step is a new risk/benefit/side effect analysis, and the application of the invention for a subgroup of patients with the long felt unsolved need by others. With that new step, a new risk/benefit/side effect analysis – as it applies to our case - we can and we pretty much have to, that is we are pretty much obligated to

administer the medication or medication combination as initial therapy for all or for substantially all patients in order to save lives (that is for the benefit of the group). This is because we do not know who in the group is affected. This was also known in the "treating appendicitis example" and was taught to me in medical school. So the benefit of the group is statistically also for the benefit of the individual patients. The key factor is the new analysis is of how we can save more lives. That was also exemplified by our example in the specification of decision making process in other areas of medicine like in the case of treating appendicitis. (Please see RCE parts re-entering the interest for the group principle with the above appendicitis example to the specification. E.g. p. 111 second paragraph).

#III / 13b-3c) The PTO errs on saying that the risk/benefit/side effect analysis was known to the art in general, so there is nothing new and inventive about that. The deciding issue is of how this principle was applied in prior art compared with our new risk/benefit/side effect analysis as in the case of our example and how that analysis can and should be applied differently after our enablement. So indeed – as the vast number of secondary factors show (and not just the mere passage of time as the PTO tried to simplify that) there is an enablement for a long felt unsolved need for initial treatment that saves lives and do provide other benefits that were not obvious in the prior art.

#III / 13b-3d) The PTO errs on saying that all treatments should be administered "as soon as possible" as this is incorrect. This theme and PTO error is repeated over and over throughout the office action. It is incorrect as the safest treatments should be administered first, and "not all treatments", while also paying attention to the clinical guidelines. In our case it was understood that if the safest treatment (antidepressant monotherapy) fails than we can use adjunct medications – as in the case of treatment resistant depression.
It was us who have shown with a new risk/benefit/side effect analysis that the safest treatment is for applying our method as initial treatment and – as for the group in whole – for substantially all patients, and this is done in order to save the most lives. No one ever done that analysis before as it was applied to in our invention.

Also, if what the PTO states about the "obviousness" of starting treatment "as soon as possible" would be true, than one could erroneously consider giving ECT for treating depression or depressive signs of a patient having a low mood score and crying after pinching his finger in between the door. This would be clinically ridiculous.

Similarly, it would be also clinically ridiculous and even dangerous administering 20-30 medications along with ECT as initial treatment based on the above PTO error that more the better and that all treatments should be administered "as soon as possible".
The PTO is considering "obvious" at the time of our invention of starting with the most aggressive treatment that is with multiple medications as soon as possible as initial therapy would be an unconvincing line of reasoning as it would disregard the risk/benefit analysis existing at the time of our invention, e.g. the risk of combining multiple medications together (risk of neuroleptics and their combination with antidepressants: utility p. 3, lines 29-32, p. 4, till line 22; see the strong teaching against in prior art (of using antipsychotics for non-psychotic, non-treatment resistant depression) (utility p. 3 lines 3-8); clinical guidelines in existence instructing of taking a divergent

path, (e.g. algorithms): January 17, 2007 Amendment pp. 95-96 and its enclosures); and in general disregarding the presented secondary factors – not just the mere passage of time. (RCE pp 32-34 2nd reply #11); January 17,2007 Amendment pp 93-99 and its enclosures). That would also mean that the PTO would find it obvious and clinically acceptable standard of care to administer all of the known antidepressants (all of them together) with all of the substances known to enhance the effects of antidepressants as in the studies showing that efficacy for the treatment resistant depression. That combination "cocktail" would include maximum dose of the antidepressants from right at the beginning, as well as giving multiple SSRIs and multiple antidepressants all at once together (since they can be used for enhancing the therapeutic efficacy of a single antidepressant – at least in some cases in treatment resistant depression). But the list for that cocktail as being "obvious" by the PTO for initial treatment would also include all of the atypical antipsychotics (and yes not just one of them but all that exist on the PTO's principle of more is the better) and not stopping the list but possible also giving for example buspirone, and pindolol, and anticonvulsant mood stabilizers (with class actually now enjoying a new FDA warning of suicide inducing risk) and Lithium (etc) all together. You can see that such a principle of << "obviousness" of starting treatment "as soon as possible" >> does not stand any clinical grounds, and it is unconvincing reasoning.

(In addition it is notable that for one of the classes of the above medications for anticonvulsant mood stabilizers the FDA is now giving a black box warning of these agents causing suicide. So the PTO declaring that our method (or this method) increasing antidepressant effect would also be inherently obvious for the treatment of suicide is not a convincing reasoning from that viewpoint.)

In other words; that is with the token of the PTO's principle of more the better or as the PTO states (e.g. as regards to Jordan from page 28):

"One of ordinary skill in the art would have recognized that these [~~two~~] therapies {or added all of them together}can be combined because they are [~~both~~] [or added all] directed toward treating the same condition, namely major depressive disorder. Combining [~~two~~] known prior art therapies is well within the ordinary and routine level of skill in the art. It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy ... as an initial therapy and/or to administer it as soon as possible. One of ordinary skill in the art would have been motivated to practice the invention in this manner because [...prior art] already disclose the treatment to be useful as a treatment for depression generally [added: but not enabling that use], **and because it is standard practice in the art to administer a therapy promptly once it is indicated**." This reasoning is unconvincing:

The above statement is **disregarding** that no enablement for our invention was shown in any of the prior art (paying attention to the applicable standard of care at the time of the invention!!!); it is also **disregarding** the strong teaching against in prior art (specifically warning of not using antipsychotics for non-psychotic, non-treatment resistant depression, as well as algorithms being present as clinical guideline instructing for a for stepwise approach using divergent path – (see teaching against: utility p. 3 lines 3-8; clinical guidelines in existence instructing of taking a divergent path, (e.g. algorithms): January 17, 2007 Amendment pp. 95-96 and its enclosures) - , as well as it is **disregarding** the risks of combining medications - (see risk of neuroleptics and their combination with antidepressants: utility p. 3, lines 29-32, p. 4, till line 22) - , and is also **disregarding** the standard practice guidelines with the risk/benefit/side effect analysis at the time of

the invention (but before our new risk/benefit analysis) and last but not least it is also **disregarding** the vast amount of secondary factors that we have presented before. (RCE pp 32-34 2nd reply #11); January 17,2007 Amendment pp 93-99 and its enclosures).
Only by disregarding all those elements could the PTO statement be considered to have any consideration for validity. If the PTO would not disregard any and all of these factors it would be clear that the PTO's reasoning is not convincing.

(The "once indicated" part is an important part – and at the time of our invention - as it was shown - it was not indicated to apply multiple medications as initial treatment for the purpose of our claims).

We cannot start treatment as soon as possible, but as indicated. The initial treatment of depression was not enabled and not indicated prior to our method; before our new inventive steps and before we have provided the necessary enablement. (See also #III/10).

#III / 13b-4) The above [#III/13b & #III/13b-3a) that is that clozapine's patent expired in 1998 that is 37 years after it was known to have antipsychotic effect that is since 1961] (see references of **Stoner SC et al Pharmacotherapy 2003; 23(6):806 second column third line from the bottom**) also shows that the PTO had an unconvincing line of reasoning. (In our case the PTO was arguing that Chappell was disclosing a broader range of diagnostic category such as depression, unipolar depression, major depressive disorder), but that does not mean that the same rules and enablement would apply for a subcategory of the diagnostic group that is for non-psychotic, non-treatment resistant unipolar depression for giving the medication or medication combination as initial treatment. This is so because the problem of previous failure by others with previously unsuggested modification for a new enablement and a new step of different risk/benefit/side effect analysis has to be applied to overcome the previously existing barriers for the clinicians to start using the invention as an initial treatment. The same was seen also with the case of clozapine. The new risk/benefit/side effect analysis for a subgroup of treatment resistant schizophrenic patients was not enabled by the 1961 patent or public knowledge on the clozapine's effect to a broader diagnostic category (that is psychosis or schizophrenia). Therefore the PTO had an unconvincing line of reasoning as to Chappell reference being enabling or making our invention obvious.

As we have stated before:

A) Rogers JL (The Complete Patent BookSphinx Publishing Napervile, IL 2003) at page 201 also notes that: "even if an act or document constitutes prior art under Sec.102, it will not bar patentability of [our] claims unless it anticipates [our] claims. ... **Anticipation only occurs if the prior art reference [is] teaching each and every element of our claims.** If [we] are successful in arguing [- and we think we gave more than enough evidence for that-] that **the reference does not anticipate [our] claims (because it is distinguishable), [we] will be removed that reference as 102(a) prior art bar to the patentability of [our] invention.**"

B) If the references are not each directed toward solving the same problem to which the invention is also directed, then the rejection should be withdrawn. (In re Rouffet, 149 F.3d 1350 [Fed. Cir. 1998].) (Rogers JL (The Complete Patent BookSphinx Publishing Napervile, IL 2003 page 223.)

C) Since the PTO's erroneous presupposition "unconvincing line of reasoning" would lead the artisan to commit malpractice the PTO did not present a convincing line of reasoning for obviousness and therefore the rejection should be withdrawn. (Ex part Clapp, 227 U.S.P.Q. 972 (Bd. Pat App. & Inter. 1985)." (Rogers JL The Complete Patent BookSphinx Publishing Napervile, IL 2003 page 219).

D) The artisan would also need solid reasons for overcoming the strong teaching away and discouraging of using the combination therapy for the purpose of our claims (and such disclosures were not given by any of the cited prior art or the PTO). "A reference teaches away when a person of ordinary skill, upon reading the reference, would be lead in a direction divergent from the path that was taken by the applicant. (In re Gurley, 27 F.3d 551 [Fed. Cir. 1994].)

E) In re Donohue, 766 F.2d 531 [Fed. Cir.1985]. "A patent or printed publication is an insufficient disclosure if it is not enabling." "The examiner cannot use references as prior art if such references have insufficient disclosures."

"A disclosure is non-enabling if it fails to place the subject matter of the claims within the possession of the public, meaning that someone with general skill in [the] field could have used the reference's description of [the] invention with their own knowledge to make [our] claimed invention themselves." (In re Wilder, 429 F.2d 447 (C.C.P.A. 1970).)

#III / 13c) The above example on clozapine shows several points and that the PTO's statements in regards to my application was incorrect and unconvincing:

A) It shows that a new risk/benefit/side effect analysis is indeed a new and inventive step.

B) Indeed this example shows that enabling of such new inventive step is protectable by intellectual property laws, and at minimum extended the patent term that would have been long expired. (This point – as a principle - is made is regardless – in case of clozapine - if the original patent owner was choosing or was not choosing to file a new patent application.)

C) It shows that a particular drug effect on a subgroup within a group is still patentable (in this case of clozapine not just for psychosis but for treatment resistant psychosis). That is congruent of Tollefson's patent application that treatment resistant depression is not the same as major depression, even though the larger group includes the smaller one, and shows that a different enablement applies. It is also evidenced that the Tollefson patent was issued, yet the Robertson publication was published long before that. (See also #VII). (Therefore Chappell would also need to enable non-treatment resistant depression, the initial treatment, as well as for substantially all patients and our other uses, with reasoning and with a new risk benefit analysis. However, that was not done therefore the rejection should be removed).

#III / 14) At page 17 the PTO states: "The intended uses recited in the instant claims, for example inhibiting the development of tolerance toward an antidepressant, providing a

neuroprotective effect, avoiding worsening of the depression, resisting suicide, avoiding suicidal ideation, and delaying or resisting relapse, are inherently present in any circumstance where the claimed drugs are administered to a patient suffering form depression, as all depressed patients are at elevated risk for suicide, and could suffer relapse after treatment."

#III / 14a) The PTO fails to show that the prior art indeed described or understood that all these uses that we claim were indeed considered inherent.
In fact the PTO disregards the vast amount of secondary factors showing to the opposite, as well as that despite the intense competition and incentives for the drug companies to find an edge in marketing; they failed to recognize the use of our claims. (RCE pp 32-34 2nd reply #11); January 17,2007 Amendment pp 93-99 and its enclosures).

#III / 14b) In addition the PTO fails to provide a convincing line of reasoning - as the new step of new risk/benefit/side effect analysis also needs to be performed along with our new enablement for the above PTO's statement getting even close to be convincing. Therefore the PTO did not show that these uses in our claims would be obvious or inherent at the time of our application.

#III / 14c) Please note that the PTO has attempted to equal anxiety with cognitive distortion to which we have responded above under #III/2a)-2f). An article by **Simon NM et al (Longitudinal outcome with pharmacotherapy in a naturalistic study of panic disorder Journal of Affective Disorders 69 (2002) 201-208)** they combine benzodiazepam alone antidepressant alone and combination of the two and conclude that the combined pharmacotherapy does not appear to provide greater protection from relapse than monotherapy (see last two lines in the abstract). Although this study is for panic (anxiety) [that the PTO erroneously considered cognitive distortion] it **would argue against that relapse prevention with multiple medications would be inherent** (and obvious in all cases) – as the PTO stated without evidence. That Simon reference therefore shows that the PTO's line of reasoning was not convincing, it is not necessarily so that combining any two medications would be preventive of relapse. Adding a second medication does not make relapse prevention inherent.
What is more interesting is that at page 204 first column second paragraph they examined if comorbid disorders such as (comorbid) depression would predict relapse and they have find that none of these variables did significantly predict relapse. (second column of that page lines 2-3). That does not support the PTO's argument of relapse "prevention" would be inherent step of applying multiple medication.
Of note is our enablement on the specific effect of the antipsychotic medications on cognitive distortion and our prior correspondence on prior art that cognitive therapy in addition to antidepressant therapy is preventive of relapse. No one ever enabled before us that indeed antipsychotics would be useful for cognitive distortions.
Therefore the PTO did not have a convincing line of reasoning of relapse "prevention" or the other steps would be inherent, and any prior art that our invention should be used (with enablement) in prior art.

#III / 14d) Furthermore, I do not understand of how the PTO can bring up as a new line of

argument now that there is inherency in the intended uses including resisting suicide, when we have specifically presented in our prior reply secondary factor(s) that would argue against such premature conclusions. Namely we have shown that most receantly the FDA have required the manufacturer of quetiapine to include a black box warningl for the risk of quetiapine causing suicide. If it would be inherent to use quetiapine (atypical antipsychotic) or antidepressant and quetiapine (atypical antipsychotic) for the treatment of depression why would it be inherent a specific action for resisting suicide, specifically if the FDA now is making the strongest warning for the opposite?

Any analysis needs to be made in light of our new risk/benefit analysis, on the benefit of the group, and that we do not know who in the group would be suicidal. Therefore there is the emphasis on the initial treatment that no one brought up or enabled before. So the intended uses including resisting suicide is not inherent, and the PTO did not give any (convincing) reasoning just a mere statement. The facts and data (secondary factors) in our prior reply in fact were talking against inherency as described above.

(Of note quetiapine is now FDA approved for bipolar disorder).

#III / 14e) In addition, <u>if</u> the PTO would be basing its statement (without explanation) that the inherency in the intended uses including resisting suicide on the false assumption that at the time of our invention it was perceived that more medications are more efficacious and are therefore safer, and therefore should be used as initial treatment for the alleged inherent purposes – that would be an unsupported assumption. The PTO is kindly reminded, that while anticonvulsant mood stabilizers are enhancing the antidepressant effect and are used for treatment resistant depression, the FDA most receantly discussed recommendation for a black box warning for suicidality of that class of medications namely the anticonvulsant mood stabilizers. Therefore the PTO stating inherency without explanation, for any of the "the intended uses recited in the instant claims, for example inhibiting the development of tolerance toward an antidepressant, providing a neuroprotective effect, avoiding worsening of the depression, <u>resisting suicide</u>, avoiding suicidal ideation, and delaying or resisting relapse" is not substantiated not only by the lack of evidence, but by the supporting secondary factors to the opposite. (RCE pp 32-34 2nd reply #11); January 17,2007 Amendment pp 93-99 and its enclosures).Therefore the rejection has to be withdrawn.

#III / 14f) The PTO has failed to bring up any prior art for the alleged inherency for any of the "the intended uses recited in the instant claims, for example inhibiting the development of tolerance toward an antidepressant, providing a neuroprotective effect, avoiding worsening of the depression, resisting suicide, avoiding suicidal ideation, and delaying or resisting relapse". In fact in the light of secondary factors mentioned in our prior reply (that is that drug companies are using every competitive edge to gain a market share, and that even a single percentage share results in 1-200 million dollars for these drug companies, such alleged inherency would have been undoubtedly spelled out and capitalized on. That was not the case at the time of our invention. Therefore the PTO's mere statement is not convincing. (See secondary factors - competitive edge (RCE pp 32-34 2nd reply #11); January 17,2007 Amendment pp 93-99 and its enclosures).

#III / 15a) Following the alleged inherency, the PTO is <u>disregarding</u> the extensive argument we have presented in our replies on why the <u>low dose</u> in the cited prior art and especially

in Chappell was not obvious. (See also January 17,2007 Amendment pp. 7-39).

#III / 15b) The PTO picks only one of the argument from the applicant's reply on the low dose issue, and basically repeats the prior PTO argument that the skilled in the art would have been motivated to use the lowest effective dose because the dangerous side effects of the antipsychotics.

#III / 15c) The PTO disregards and makes no comment on the applicant's prior comment on the low dose argument as mentioned above. (See also January 17,2007 Amendment pp. 7-39).

#III / 15d) In addition the PTO fails to support his statement with any prior art that would show that the cited antipsychotic side effects (and namely the dangerous ones like TD (tardive diskinesia) and NMS (neuroleptic malignant syndrome) would have been eliminated by using the lowest effective dose. The PTO also did not show any prior art of any risk benefit analysis showing that the "low dose" antipsychotics contemplated for the treatment of depression that was indeed discussed in any prior art in regards of the risk benefit side effect analysis to have significantly less side effects as regards of the danger of TD (tardive diskinesia) and NMS (neuroleptic malignant syndrome).

#III / 15e) The PTO also failed to show that **A)** the strong teaching against of using antipsychotics in non-psychotic, non-treatment resistant depression would be exempt in low dose form that strong teaching against, or **B)** that a low dose (that the PTO declares the skilled in the art would have been motivated using) would for some reason null and void **both** that strong teaching against **and** the other guidelines and algorithms instructing of taking a divergent path and start treatment with monotherapy. In absence of that the PTO did not present a convincing line of reasoning on the motivation of the skilled in the art to use our method, and the rejection has to be withdrawn.

#III / 15f) 15a) to 15e) and the answers given in prior replies (see January 17,2007 Amendment pp. 7-39) clearly show that the low dose was not enabled in prior art as for the initial treatment of depression with antipsychotics or antipsychotic antidepressant combination, or that the use of low dose would have been obvious for the purposes of our claims for the skilled in the art. The PTO also disregards and makes no comment on the vast amount of secondary factors (much more than the mere passage of time) that we have presented in our prior replies. (RCE pp 32-34 2nd reply #11); January 17,2007 Amendment pp 93-99 and its enclosures). Therefore the PTO did not present a convincing line of reasoning and the rejection has to be withdrawn.

#III / 16a) at page 17 the PTO tries to imply that Chappell disclosing broad range of conditions such as major depressive disorder or unipolar depression would include the "non-treatment resistant and non-psychoic depression" as these fall within the broader categories of Chappell. This is not so as we have demonstrated that extensively with the clozapine example under #III/13) and also and in particular under III/13C section C). The PTO also errs calling Chappell's broader range of conditions as "given this disclosure", when Chappell did **not enable** his method for

the smaller group of "non-treatment resistant and non-psychoic depression".

#III / 16b) Furthermore Chappell did not enable the method for initial treatment.

#III / 16c) In fact in the response to argument part line 3, the PTO brings up (and therefore acknowledges) that the applicant argues that Chappell did not provide enablement, but the PTO never disputes that argument or nowhere shows that indeed that enablement was present in the Chappell reference. As we have stated in our earlier replies: In re Donohue, 766 F.2d 531 [Fed. Cir.1985]. "A patent or printed publication is an insufficient disclosure if it is not enabling." **"The examiner cannot use references as prior art if such references have insufficient disclosures."** "A disclosure is non-enabling if it fails to place the subject matter of the claims within the possession of the public, meaning that someone with general skill in [the] field could have used the reference's description of [the] invention with their own knowledge to make [our] claimed invention themselves." (In re Wilder, 429 F.2d 447 (C.C.P.A. 1970).) We have shown above from #III/1) on of why Chappel was not enabling and why it failed to place the subject matter of the claims within the possession of the public. We have also shown that the PTO's reasoning was unconvincing.

#III / 16d) The PTO makes a statement that Chappell's method would have been obvious to be applied for cases not demonstrating treatment resistance or psychosis, but fails to support that statement. In regards to our prior extensive arguments of why these categories require additional enablement and the new risk/bebefit/side effect analysis for the use of our claims, the PTO does not make any comments here. (These include to overcome the strong teaching against and the clinical guidelines (algorithms) that instruct to take a divergent path). Just that the Chappell reference did not specifically said that the treatment should be specifically directed to treatment resistance it does not imply that that enabled their method for other subgroups, for the use of our claims, or that the person with ordinary skill in the art would have been able to use that method without specific enablement for the groups and for the uses in our claims. [See also #III/13, including III/13-C section C); #III/10 and #VII/8].

#III / 16d-1) It is notable that the PTO repeatedly brings up that it finds it critical in our case that no working examples were presented in my application [even though it was still enabled]. In contrast the PTO implies that the Chappell reference without working example or without enablement for the pertaining subgroup of "non-treatment resistant and non-psychoic depression" and specifically as for initial treatment would be OK and acceptable in the Chappell's case. Again, we see a discrepancy in how our case is handled. (We had mentioned before that the PTO's requirement for patentability is not the working example, but enablement that we have provided with our extensive written specification, clear description, and hypothetical cases). No studies were mentioned in the Chappell reference for non-treatment resistant and non-psychotic depression.

#III / 16d-2) It is notable that the PTO had withdrawn prior arguments in case of Tollefson on the basis of realizing that the Tollefson references did not had any studies (or enablement) on non-treatment resistant depression. Why would the Chappell reference deserve a different treatment as regards to enablement requirement from the PTO? As we have shown the PTO's reasoning was unconvincing.

#III / 17) The PTO's following argument that this applicant did not direct the clinician not to administer the therapy to psychotic or treatment resistant cases is irrelevant as for supporting the above mentioned erroneous PTO logic, as it had been already known and had been enabled in prior art that the combination therapy for these uses are effective. Therefore it would have been improper to direct the clinicians of not to use the method for something we were specifically **not claming** (and excluded from our claims), and for which it was known that the prior art method was effective. Using our method for something known in prior art (and specifically excluding these uses in our claims) is neither a malpractice nor does it require enablement for non-claimed items. The reverse is not true in Chappell's case, therefore "it is not the same scope" as the PTO insists that it is. The Chappell reference failed to provide the enablement requirement for the subgroups mentioned and for the use of our claims.
Therefore the PTO failed to show a convincing line of evidence in support of its argument.

As we have stated before:

A) Rogers JL (The Complete Patent BookSphinx Publishing Napervile, IL 2003) at page 201 also notes that: "even if an act or document constitutes prior art under Sec.102, it will not bar patentability of [our] claims unless it anticipates [our] claims. ... **Anticipation only occurs if the prior art reference [is] teaching each and every element of our claims.** If [we] are successful in arguing [- and we think we gave more than enough evidence for that-] that **the reference does not anticipate [our] claims (because it is distinguishable), [we] will be removed that reference as 102(a) prior art bar to the patentability of [our] invention.**"

B) If the references are not each directed toward solving the same problem to which the invention is also directed, then the rejection should be withdrawn. (In re Rouffet, 149 F.3d 1350 [Fed. Cir. 1998].) (Rogers JL (The Complete Patent BookSphinx Publishing Napervile, IL 2003 page 223.)

C) Since the PTO's erroneous presupposition "unconvincing line of reasoning" would lead the artisan to commit malpractice the PTO did not present a convincing line of reasoning for obviousness and therefore the rejection should be withdrawn. (Ex part Clapp, 227 U.S.P.Q. 972 (Bd. Pat App. & Inter. 1985)." (Rogers JL The Complete Patent BookSphinx Publishing Napervile, IL 2003 page 219).

D) The artisan would also need solid reasons for overcoming the strong teaching away and discouraging of using the combination therapy for the purpose of our claims (and such disclosures were not given by any of the cited prior art or the PTO). "A reference teaches away when a person of ordinary skill, upon reading the reference, would be lead in a direction divergent from the path that was taken by the applicant. (In re Gurley, 27 F.3d 551 [Fed. Cir. 1994].)

E) In re Donohue, 766 F.2d 531 [Fed. Cir.1985]. "A patent or printed publication is an

insufficient disclosure if it is not enabling." "The examiner cannot use references as prior art if such references have insufficient disclosures."

"A disclosure is non-enabling if it fails to place the subject matter of the claims within the possession of the public, meaning that someone with general skill in [the] field could have used the reference's description of [the] invention with their own knowledge to make [our] claimed invention themselves." (In re Wilder, 429 F.2d 447 (C.C.P.A. 1970).)

Therefore the rejection has to be withdrawn.

From page 18
Claims 106-108 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chappell et al. (US patent application 10/001827, Pub. Number 2002/0094986 A 1, of record in previous office action) in view of Berman et al. (Reference of record in previous action) The disclosure of Chappell et al. is discussed above. Chappell et al. does not disclose a method in which the antidepressant is ketamine.

Berman et al. discloses that ketamine exerts antidepressant effects in human patients. (p. 351, second paragraph, right column, p. 352, left column, last paragraph, p. 353, right column, first paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to use ketamine as the antidepressant in the method of Chappell et al. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Berman et al. reveals that ketamine is useful for the same purposes as the antidepressants recited by Chappell et al. One of ordinary skill in the art would reasonably have expected success because Ketamine is already known to be useful as an antidepressant.

Thus the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's argument, filed August 27, 2007, as applied to the above rejection, has been fully considered and not found to be persuasive to remove the rejection. Applicant argues that ketamine has severe side effects and therefore would not be used by

one of ordinary skill in the art as an antidepressant. However, as discussed above, according to MPEP 2123, nonpreferred embodiments of the prior art are equally valid as prior art. "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." In re Gurley, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994) The mere fact that one of ordinary skill in the art would have known of compounds that produced fewer side effects than ketamine does not mean that the use of ketamine as an antidepressant is non-enabled. In fact, Berman et al. discloses a successful clinical treatment of depression in human subjects using ketamine, which is sufficient enabling disclosure to practice this therapeutic method.

Furthermore, Applicant argues that the failure of those of ordinary skill in the art to use ketamine as an antidepressant in the five years since the publication of the cited references is indicative of secondary factors proving nonobviousness. According to *Iron Grip Barbell* Co., *Inc. v. USA Sports, Inc.*, 392 F.3d 1317, 1322,73 USPQ2d 1225, 1228 (Fed. *Cir.* 2004), "[a]bsent a showing of a long-felt need or the failure of others, the mere passage of time without the claimed invention is not evidence of nonobviousness." 392 F.3d at 1324-25, 73 USPQ2d at 1229-30. See MPEP 2144.05 (B.III). Applicant does not show a long-felt need for a new antidepressant, or the failure of others to use ketamine as an antidepressant. In fact, Applicant's disclosure provides no new data, information, or reasoning about ketamine that would contribute to what is known in the art about this drug, or to indicate that ketamine is particularly useful in the claimed combination therapy. Therefore there is nothing novel, non-obvious, or unexpected about Applicant's proposed use of ketamine in the claimed invention.

For these reasons the rejection is deemed proper and maintained.

#IV of third reply (first reply after RCE):
The PTO said: Claims 106-108 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chappell et al. **in view of** Berman.

My reply:

#IV / 1) Previously we have extensively argued that our claims would be patentable over Chappell, and so it would also be in view of Berman. That by itself would sufficiently answer this rejection. (And therefore the rejection should be withdrawn).

#IV / 2) In response to the applicant's reply in the RCE, the PTO cites MPEP 2123 and states that "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." In re Gurley, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994). However, the PTO disregards that the deciding

question is not that the method is somewhat inferior, but that a new risk/benefit/side effect analysis has to be performed, and also that there was no prior art stating that ketamine to be used as initial treatment. Even as Berman enabled ketamine as an antidepressant, but it was not enabled as a first choice, as an initial treatment with an antipsychotic for the reasons we enabled our method as part of the combination treatment. [Please also refer back to #III/13) on the analogy of the new risk benefit analysis in regards to clozapine].

#IV / 3) Furthermore the PTO cites "*Iron Grip Barbell* Co., *Inc. v. USA Sports, Inc.*, 392 F.3d 1317, 1322,73 USPQ2d 1225, 1228 (Fed. *Cir.* 2004), "[a]bsent a showing of a long-felt need or the failure of others, the mere passage of time without the claimed invention is not evidence of nonobviousness." 392 F.3d at 1324-25, 73 USPQ2d at 1229-30. See MPEP 2144.05 (B.III)." This citation by the PTO is applied out of context, **as if** the mere passage of time – as the only factor - would have been presented to make the argument for nonobviousness. This was simply not the case. The PTO is kindly reminded to the vast amount of secondary factors that we have presented along with a copy of the pertinent pages of a patent law book drawing attention that indeed the secondary factors are important in deciding patentability and non-obviousness. (RCE pp 32-34 2nd reply #11); January 17,2007 Amendment pp 93-99 and its enclosures).

The PTO is also kindly reminded that The PTO is conditioning its response on the false assumption that our claims would not be patentable over Chappel. As shown previously, this is not the case. In addition, and in part also in contrast to the above "*Iron Grip Barbell* Co" citation, the PTO had acknowledged the importance of the secondary factors in the "interview".

#IV / 4) The PTO erroneously makes several incorrect statements, that includes that "Therefore there is nothing novel, non-obvious, or unexpected about Applicant's proposed use of ketamine in the claimed invention". The PTO is kindly reminded that the use of ketamine is in the claims and specification and is described as an antidepressant to be used as adjunct with antipsychotics for synergistic antidepressant effect, and as initial treatment for the purposes of our claims. Indeed, we have argued and shown the novelty and unobviousness and the long felt need of our invention as for the combination therapy. In fact so many things were unexpected, and novel and unobvious in our application that the FDA directors many years later were still perplexed about their inability to give answer to questions for which we gave a solution with long-felt unsolved needs. We have described this with the secondary factors. So the PTO's statement is really not substantiated as regards to our claims.

-- I have not seen a clinically convincing line of argument by the PTO of how ketamine could be used initial treatment showing obviousness, or prior art on new risk/benefit side effect analysis. What was said with clozapine above also stands here [#III /13)].

From page 20

The following new grounds of rejection are introduced: •

Claim Rejections. 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless (b) the invention was patented or described in a printed pUblication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 126-128 are rejected under 35 U.S.C. 102(b) as being anticipated by Robertson et a!. (Reference of record in PTO-892) Robertson et a!. discloses a number of studies of the antidepressant activities of major tranquilizers (also known as typical antipsychotics). (p. 173, last paragraph) In particular, perphenazine and combinations of perphenazine with amitriptyline were used in treating patients suffering from depression, including non-psychotic depression. (p. 179, paragraphs 4-5) Perphenazine was found in one study to be particularly effective, while a combination of perphenazine and amitriptyline was found to be effective for treating other types of depression. It is noted that anxiety is reasonably considered to be a cognitive distortion as it involves unreasonable patterns of thought, namely excessive or irrational worry and exaggeration of problems or threats. Flupenthixol, (p. 183, paragraphs 4-6) and sulpride, (p. 185, paragraphs 1-2) are also seen to possess antidepressant activity. The intended uses recited in the instant claims, for example inhibiting the development of tolerance toward an antidepressant, providing a neuroprotective effect, avoiding worsening of the depression, resisting suicide, avoiding suicidal ideation, and delaying or resisting relapse, are **inherently present** in any circumstance where the claimed drugs are administered to a patient suffering form depression, as all depressed patients are at elevated risk for suicide, and could suffer relapse after treatment.

Therefore the claimed invention is anticipated by Robertson et al.

#V of third reply (first reply after RCE): (see also #III above)

The PTO had new grounds of rejection: "Claims 126-128 are rejected under 35 U.S.C. 102(b) as being anticipated by Robertson. " These claims pertain to the treatment of cognitive distortions.

My reply:

#V / 1) These claims pertain to the treatment of cognitive distortions, and we have addressed that above including the PTO's erroneous conclusion of equaling anxiety with cognitive distortion. (Please see #III 2a) to 2f) above). That **[#III 2a) to 2f) above**] by itself would sufficiently answer the issue and remove this rejection.

#V / 2) The PTO shows an unconvincing line of reasoning, since if what the PTO claims as an anticipation by Robertson would be true for my application, than it would have also applied to the Tollefson patent and that would not have been approved by the PTO. Yet as it is known the Tollefson patent was issued. (Of note the Tollefson patent was cited earlier by the PTO in an earlier office action, with the rejection later withdrawn.)
Therefore the above claims and my invention also could not be anticipated by Robertson.

In other words: If what the PTO claims as an anticipation by Robertson would be true in anticipating our claims, than how come a different standard would have been applied for Tollefson's patent that was issued? (We have raised in our earlier replies concerns on different standard being applied against us as a small entity inventor). The PTO cannot use double standards. However, we truly believe, that the PTO in citing an anticipation by Robertson was erroneous as it is also evidenced by #V/1) above and the answers below.

#V / 3) Additionally and most importantly, it is also notable, that the PTO makes his assumption that the risk/benefit analysis and the standard of care stagnated over the decades, and that it does not change. The PTO is kindly reminded that as new developments were seen (like the introduction of effective newer antidepressants and SSRI's with safety profile as regards to overdose compared to the lethality of tricyclic and tetracyclic antidepressant overdose) the current standard of care used at that time was also changing. That is that the risk/benefit/side effect analysis and the indication to use and of how to use medications also did change.
Specifically, new guidelines were introduced (including algorithms instructing of taking a divergent path, and teaching against using antipsychotics in non-psychotic-non-treatment resistant depression). Please see our specification in our utility as well as our extensive citations in our prior reply. (See risk of neuroleptics and their combination with antidepressants: utility p. 3, lines 29-32, p. 4, till line 22, teaching against: utility p. 3 lines 3-8; clinical guidelines in existence instructing of taking a divergent path, (e.g. algorithms): January 17, 2007 Amendment pp. 95-96 and its enclosures).

It is also notable, that we have excluded the antidepressants used in the Robertson article.
Therefore, at the time of our invention the skilled in the art could **not** have applied our invention for the purpose of our claims relying on the Robertson reference, ignoring newer guidelines, and the current standard of care of the time, without having a good reason and enablement at hand for our techniques. That is without giving sufficient and detailed guidance (similar to ours) in explaining of what specific benefit our method would give to the patients overriding the (old) risk/benefit side

effect analysis that was used at the time of our invention the skilled in the art could not have used our technique. Therefore our invention was not anticipated by the skilled in the art at the time of our invention based on the Robertson article.

#V / 3b) In addition in our utility application we specifically drew attention to that Robertson article and the existing difference to our application.

That included that the first drug to treat mental illness was an antipsychotic, and in lack of antidepressants at that time [using the standard of care and the risk benefit analysis of the time] it was not surprising that the typical antipsychotics were tried for the treatment of depression. We have also said that this practice was abandoned as newer treatments became available. (utility page 1, lines 25-32, p 2, lines 1-9).

We have also discussed the methodological problems in Robertson article that including that many of patients were diagnosed with comorbid anxiety (called at that time mixed anxiety). [Please refer back to utility p. 2 lines 25-32, p. 3 lines 1-2, and to our prior reply that the PTO already accepted - RCE pages 6-7 2nd reply 1-A) & 1-B) and RCE pages 9 section a) and page 11 section e) for example].

Therefore our invention was not anticipated by the skilled in the art at the time of our invention based on the Robertson article.

#V / 4) It is also of note that amitriptiline an older type triciclic antidepressant is not listed in claims 126-128.

As far as older typical antipsychotic use we have not claimed them for monotherapy, and initial treatment. We did specify the relative risk benefit analysis for cases when newer atypical antipsychotics are not available, (as a second choice) they still have a value in combination with newer antidepressants.

#V / 5) We have discussed above [#III 14a)-14f)] of why the cited uses in our claims are not inherent.

#V / 6) Under #III above we have addressed of why the initial treatment, and also the low dose would not be obvious; and that reply would be also applicable here.

From page 21

Claim Rejections* -35 *USC* § *103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness

rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title. if the differences between the subject matter sought to be patented and the prior art are such that the sUbject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said sUbject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5, 16, 17,20,21,24,25,28,29,32-35,64,75,76,79,80,83,84,87,88, 91-94, 123, and 125 are rejected under 35 U.S.C. 103(a) as being unpatentable **over Chappell** et al. (US patent application 10/001827, Pub. Number 2002/0094986 A 1, of record in previous office action) as applied to claims 1-4,6,10-15,18,22,26,30,36-38, 41-43,48,49,51-63,66,70-74,77,81,85,89,95-105, and 109-122,124, and 126-30 above, and further in view of Schmidt et al. (Reference of record in PTO-892) The disclosure of Chappell et al. is discussed above. Chappell et al. does not disclose a method using ziprasidone, risperidone, or quetiapine as the antipsychotic agent.

Schmidt et al. discloses the affinities of a number of antipsychotic drugs for the D4 receptor. (p. 198. table 1) In particular, ziprasidone, risperidone, olanzapine, and quetiapine are all shown to have affinity for the D4 receptor.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use ziprasidone, risperidone, or quetiapine as the dopamine D4 antagonist in the invention of Chappell et al. One of ordinary skill in the art would have recognized that these compounds possess the same biological activity, namely D4 antagonism, required by the invention of Chappell et al., and can thus be used as therapeutic agents in this invention. Applying a known thecapeutic agent in this way to a known therapeutic method, is part or the ordinary and routine level of skill in the art.

Thus the invention taken as a whole is *prima facie* obvious.

#VI of third reply (first reply after RCE): (see also #III) and in view of...
The PTO said that: Claims 5, 16, 17,20,21,24,25,28,29,32-35,64,75,76,79,80,83,84,87,88, 91-

94, 123, and 125 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chappell, as applied to claims 1-4,6,10-15,18,22,26,30,36-38, 41-43,48,49,51-63,66,70-74,77,81,85,89,95-105, and 109-122,124, and 126-30 above, and further in view of Schmidt et al. (Schmidt et al. discloses the affinities of a number of antipsychotic drugs for the D4 receptor. (p. 198. table 1) In particular, ziprasidone, risperidone, olanzapine, and quetiapine are all shown to have affinity for the D4 receptor.)

My reply:
Since under **#III** above we have successfully and sufficiently argued that our invention is patentable over Chappell, the conclusion of "Thus the invention taken as a whole is *prima facie* obvious" is also incorrect. Therefore the rejection should be removed. (This is particularly true **in view of Kramer** see **#III/1** above).

(Please also refer to Reply 1 and Reply2 – RCE that are also explicitly incorporated herein).

From page 22

Claims 5, 9, 16, 20, 24, 28, 64, 75, 79, 83, 87, and 125 are rejected under 35 U.S.C. 103(a) as being unpatentable **over Chappell** et al. (US patent application 10/001827, Pub. Number 2002/0094986 A1, of record in previous office action) as applied to claims 1-4,6,10-15,18,22,26,30,36-38,41-43,48,49,51-63, 66,70-74, 77,81,85,89,95-105, and 109-122, 124, and 126-30 above, and further in view of Roth et al. (Reference of record in PTO-892) The disclosure of Chappell et al. is discussed above. Chappell et al. does not disclose a method using risperidone, trifluoroperazine, or zotepine as the antipsychotic agent.

Roth et al. discloses the affinities of a number of antipsychotic drugs for the D4 receptor. (p. 366, table 1) In particular, risperidone, olanzapine, trifluoroperazine and zotepine are all shown to have affinity for the D4 receptor.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use risperidone, trifluoroperazine, or zotepine as the dopamine D4 antagonist in the invention of Chappell et al. One of ordinary skill in the art would have recognized that these compounds possess the same biological activity, namely D4

antagonism, required by the invention of Chappell et al., and can thus be used as therapeutic agents in this invention. Applying a known therapeutic agent in this way to a known therapeutic method, is part or the ordinary and routine level of skill in the art.
Thus the invention taken as a whole is *prima facie* obvious.

#VI of third reply (first reply after RCE): (see also #III)

The PTO said: Claims 5, 9, 16, 20, 24, 28, 64, 75, 79, 83, 87, and 125 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chappell, as applied to claims 1-4,6,10-15,18,22,26,30,36-38,41-43,48,49,51-63, 66,70-74, 77,81,85,89,95-105, and 109-122, 124, and 126-30 above, and further in view of Roth et al. (Roth et al. discloses the affinities of a number of antipsychotic drugs for the D4 receptor. (p. 366, table 1) In particular, risperidone, olanzapine, trifluoroperazine and zotepine are all shown to have affinity for the D4 receptor.)

My reply:
Since under #III above we have successfully and sufficiently argued that our invention is patentable over Chappell, the conclusion of "Thus the invention taken as a whole is *prima facie* obvious" is also incorrect. Therefore the rejection should be removed. . (This is particularly true **in view of Kramer** see **#III/1** above).

(Please also refer to Reply 1 and Reply2 – RCE that are also explicitly incorporated herein).

From page 23

Claims 1-3, 9,11-15,37,38,41-43,48,49,53-62,69-74,96-105, and 129 are rejected under 35 U.S.C. 103(a) as being unpatentable **over Robertson** et al. (Reference of record in PTO-892) as applied to claims 126-128 above, and further in view of the Merck Manual of Diagnosis and Therapy, Seventeenth Edition. (Reference included with PTO-892, herein referred to as Merck) The disclosure of Robertson et al. is discussed above. Robertson et *al.* does not disclose a therapy comprising a combination of a typical antipsychotic with a newer antidepressant. (Ie. an antidepressant that is not a tricyclic or tetracyclic antidepressant or a MAO inhibitor) Robertson et al. does not explicitly disclose a method of

administering the claimed treatments as an initial treatment, as soon as possible, or upon presentation to a physician or other health care provider, or a method comprising administering a low dose of the antipsychotic.

Merck discloses a list of antidepressants useful for treating major depressive disorder. (p. 1534, table 189-6) These antidepressants include various antidepressants recited in the instant claims such as Clomipramine, fluoxetine, sertaline, paroxetine, and fluvoxamine.

It would have been **obvious** to one of ordinary skill in the art **at the time of the invention** to co-administer the antidepressants of Merck with the typical antipsychotics of Robertson et al. One of ordinary skill in the art would have recognized that these two therapies can be combined because they are both directed toward treating the same condition, namely major depressive disorder. Combining two known prior art therapies is well within the ordinary and routine level of skill in the art.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy disclosed by Robertson et al. as an initial therapy and/or to administer it as soon as possible. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Robertson et al. and Merck already disclose the treatment to be useful as a treatment for depression generally, and because it is standard practice in the art to administer a therapy promptly **once it is indicated**. One of ordinary skill in the art would reasonably have expected success because choosing a particular therapeutic regimen from among the various options available in the prior art is within the routine and ordinary level of skill in the art.

Finally, it would have been **obvious** to one of ordinary skill in the art to administer the antipsychotic in a **low** dose. One of ordinary skill in the art would have been motivated to administer the lowest effective dose of the drug because of the well known side effects of typical

antipsychotic drugs. One of ordinary skill in the art would have reasonably been able to adjust the dosage of the compounds administered to achieve the optimal result while minimizing toxicity from the drugs themselves.

Thus the invention taken as a whole is *prima facie* obvious.

#VII of third reply (first reply after RCE): (see also #III) [and in view of...]

The PTO said: Claims 1-3, 9,11-15,37,38,41-43,48,49,53-62,69-74,96-105, and 129 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robertson et al. as applied to claims 126-128 above, and further in view of the Merck Manual of Diagnosis and Therapy, Seventeenth Edition.

My reply:

#VII / 1) The PTO shows an unconvincing line of reasoning, since if what the PTO claims as an anticipation by Robertson would be true for the application of my claims, than the same rules would have also applied to the Tollefson patent which would not have been approved by the PTO. Yet as it is known the Tollefson patent was issued. (Of note the Tollefson patent was cited earlier by the PTO in an earlier office action, with the rejection later withdrawn.)
Therefore the above claims and my invention also could not be anticipated by Robertson.

In other words: If what the PTO claims as an anticipation by Robertson would be true in anticipating our claims, than how come a different standard would have been applied for Tollefson's patent that was issued? (We have raised in our earlier replies concerns on different standard being applied against us as a small entity inventor). The PTO cannot use double standards. However, we truly believe, that the PTO in citing an anticipation by Robertson was erroneous as it is also evidenced by the answers below.

#VII / 2) Please also refer to #V, and in particular to #V/3 of which reply is incorporated herein. Since the publication of Robertson reference new development in psychopharmacology made prior treatments (as for risk benefit etc) obsolete and the standard of treatment and clinical guidelines did change. So it was not obvious the time of our invention to apply the Robertson reference in anticipating our treatment at least until the new risk benefit analysis was enabled by us with the other guidelines. [Please see also **#III/13, #III/13b-1a & 1b); #V/3; and VII/8**].

The PTO makes his assumption that the risk/benefit analysis and the standard of care stagnated over the decades, and that it does not change. The PTO is kindly reminded that as new developments were seen (like the introduction of effective newer antidepressants and SSRI's with safety profile as regards to overdose compared to the lethality of tricyclic and tetracyclic antidepressant overdose) the current standard of care used at that time was also changing. That is that the risk/benefit/side effect analysis and the indication to use and of how to use medications also did change.

Specifically, new guidelines were introduced (including algorithms instructing of taking a divergent path, and a strong teaching against using antipsychotics in non-psychotic-non-treatment resistant depression). Please also see #III/13b-1a) % 1b); and our specification in our utility as well as our extensive citations in our prior reply (risk of neuroleptics and their combination with antidepressants: utility p. 3, lines 29-32, p. 4, till line 22, teaching against: utility p. 3 lines 3-8; clinical guidelines in existence instructing of taking a divergent path, (e.g. algorithms): January 17, 2007 Amendment pp. 95-96 and its enclosures).

It is also notable, that we have excluded the antidepressants used in the Robertson article. Therefore at the time of our invention the skilled in the art could not have applied our invention for the purpose of our claims relying on the Robertson reference, ignoring new guidelines and the current standard of care of the time, without having a good reason and enablement for our techniques. That is the skilled in the art would have to overcome the strong teaching against (using antipsychotics) a recommendation that was the accepted standard after the Robertson publication based on the risk/benefit analysis at the time of our application. The skilled in the art would have to also give sufficient and detailed guidance (similar to ours) in explaining of what specific benefit it would give to the patients overriding the risk/benefit side effect analysis that was used at the time of our invention. The skilled in the art would have to come up with an overwhelming benefit. The Robertson article and any other prior art is missing on our new risk/benefit analysis for the subgroup of a patients. (As shown before with the clozapine example that can be the basis of a new invention and new patent terms even with the knowledge of the clozapine's action. See #III/13). Therefore our invention was not anticipated by the skilled in the art at the time of our invention based on the Robertson article.

#VII / 2b) In addition in our utility application we specifically drew attention to that Robertson article and the difference to our application.

That included that the first drug to treat mental illness was an antipsychotic, and in lack of antidepressants at that time [using the standard of care and the risk benefit analysis of the time] it was not surprising that the typical antipsychotics were tried for the treatment of depression. We have also said that this practice was abandoned as newer treatments became available. (utility page 1, lines 25-32, p 2, lines 1-9).
We have also discussed the methodological problems in Robertson article that including that many of patients were diagnosed with comorbid anxiety (called at that time mixed anxiety).). [Please refer back to utility p. 2 lines 25-32, p. 3 lines 1-2, and to our prior reply that the PTO already accepted - RCE pages 6-7 2nd reply 1-A) & 1-B) and RCE pages 9 section a) and page 11 section e) for example].
Therefore our invention was not anticipated by the skilled in the art at the time of our invention based on the Robertson article.

#VII / 3) It is also of note that amitriptiline an older type triciclic antidepressant is not listed in claims 126-128.

As far as older typical antipsychotic use we have not claimed them for monotherapy, and initial treatment. We did specify the relative risk benefit analysis for cases when newer atypical

antipsychotics are not available, (as a second choice) they still have a value in combination with newer antidepressants.

#VII / 4) Under **#III** above we have addressed of why the initial treatment, and also the low dose would not be obvious; and that reply would be also applicable here. Therefore the rejection should be withdrawn for the same reasons.

#VII / 5) We have discussed above [#III 14a)-14f)] of why the cited uses in our claims are not inherent. These claims therefore would be (also) allowable.

#VII / 6) We have also discussed under #III/2a) to 2f) and under #V of why the cited uses for cognitive distortion were not anticipated and were not obvious. Even if for any unforeseen and other than above mentioned reasons by the PTO our invention would be rejected; our invention should still be accepted based on our invention targeting cognitive distortions. However as our reply shows the PTO's rejection as presented should be withdrawn, as it did not present a convincing line of evidence.

#VII / 7) The PTO has disregarded the vast amount of secondary factors – other than the mere passage of time (and as it was also brought up e.g. under #III above) in my support of my invention. (See also RCE pp 32-34 2nd reply #11); January 17,2007 Amendment pp 93-99 and its enclosures).

#VII / 8) Anticipation by Robertson could not occur also (based on the new risk/benefit analysis) as neither Robertson nor the PTO recognized the value of and need to apply our method for substantially all and all patients (within our claims). Even though – as the PTO referencing us – we use a may and no a must use our method, from our specification it becomes clear that **a)** the risk/benefit analysis needs to be discussed with the patient, **b)** that patient right issues would not allow to use our method against the will of the patient, **c)** and that the skilled in the art must also look the benefit of the group [since we do not know who in the group would be affected – e.g. by suicide – as it was explicitly described with the analogy of how we were treating appendicitis]. **d)** Our specification also drew attention to the discrepancy that in prior art no one paid attention that if the patient (with personality disorder) bothers the psychiatrist than we psychiatrists gave them multiple of psychotropic medications [sometimes 4 or 5 of them at the same time], but if the patient with depression with much higher risk of suicide die quietly nobody seems to be bothered and our field hides under the risks and side effects of the antipsychotics of why these cannot be used. This is unacceptable, and that was one of our reasons and one of our clinical guidance for enablement. It is therefore understood that really our method is (also) for substantially all and all patients as an initial treatment (within our diagnostic category). This was nowhere anticipated by Robertson either.
(For the above and for the discrepancy in the statistics of the suicide between the two patient group please also refer to our specification). (See parts re-entered with RCE to our specification page 112 fourth paragraph).

[See also clozapine example under #III 13) for the value of the new risk/benefit analysis; and #III/13b-3d) last 3 paragraphs and #III/10.]

#VII / 9) As we mentioned under #VII/ 1) to VII/ 8) the PTO had an unconvincing line of reasoning. If what the PTO claims as an anticipation by Robertson would be true for my application, than it would have also applied to the Tollefson patent and that would not have been approved by the PTO. Yet as it is known the Tollefson patent was issued.
For all these reasons the above claims and my invention also could not be anticipated by Robertson.

From page 25

Claims 106-107 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robertson et al. (Reference of record in PTO-892) in view of Berman et al. (Reference of record in previous action) The disclosure of Robertson et al. is discussed above. Robertson et al. does not disclose a method in which the antidepressant is ketamine.

Berman et al. discloses that ketamine exerts antidepressant effects in human patients. (p. 351, second paragraph, right column, p. 352, left column, last paragraph, p. 353, right column, first paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to use ketamine as an antidepressant in combination with a typical antipsychotic recited in the method of Robertson et al. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Berman et al. reveals that ketamine is useful for the same purposes as the therapies recited by Robertson et al., namely treating depression. One of ordinary skill in the art would reasonably have expected success because Ketamine is already known to be useful as an antidepressant.
Thus the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's argument, filed August 27, 2007, as applied to the above rejection, has been fully considered and not found-to be persuasive to remove the rejection, for reasons recited as regards the rejection over Chappell et al. in

view of Berman et al.

#VIII of third reply (first reply after RCE): (see also #III)
The PTO said: Claims 106-107 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robertson et al. (Reference of record in PTO-892) in view of Berman et al.

My reply:

#VIII / 1) PTO did not give reason for rejection in the "response to argument" part at page 26. However this was a new rejection (so no response could have been given earlier).

#VIII / 2) Since under **#VII** above we have successfully and sufficiently argued that our invention is patentable over Robertson, the conclusion of "Thus the invention taken as a whole is *prima facie* obvious" is also incorrect. Therefore the rejection should be removed.

(Please also refer to #IV, and #VII, above also pertaining in view of Berman and Reply 1 and Reply2 – RCE that are also explicitly incorporated herein also in regards to what we have said about ketamine).

From page 26

Claims 1,2,4,5,6, 10-14, 16-18, 20-22, 24-26, 28-30, 32-38, 41-43, 48,49,51-64,66,70-77,79-81,83-85,87-89,91-105,109-122, and 124-129 are rejected under 35 U.S.C. 103(a) as being unpatentable **over Pivac** et al. (Reference included with PTO892) in view of Merck (Reference included with PTO-892) Pivac et al. discloses that atypical antipsychotics such as risperidone or olanzapine, should be coadministered with selective serotonin reuptake inhibitors, because they produce a synergistic effect. (p. 236, left column, last paragraph, right column first paragraph) Pivac et al. does not disclose a therapeutic method using the specific SSRIs fluoxetine, paroxetine, sertaline, or fluvoxamine, or the atypical antipsychotics ziprasidone or quetiapine. Pivac et al. does not explicitly disclose a method of administering the claimed treatments as an initial treatment,

as soon as possible, or upon presentation to a physician or other health care provider, or a method comprising administering a low dose of the antipsychotic.

Merck discloses a list of antidepressants useful for treating major depressive disorder. (p. 1534, table 189-6) These antidepressants include various antidepressants recited in the instant claims such as Clomipramine. fluoxetine, sertaline, paroxetine, and fluvoxamine. Merck et al. also discloses a listing of atypical antipsychotics, including clozapine, risperidone, olanzapine, quetiapine, sertindole, and ziprasidone. (p. 1570, table 193-4)

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the various SSRIs and atypical antipsychotics disclosed by Merck in the method of Pivac et al. One of ordinary skill in the art would have recognized that the specific compounds disclosed by Merck fall within the broad classes described by Pivac et al., and can thus be used in the disclosed method. Substituting these known prior art compounds in a known prior art method is well within the ordinary and routine level of skill in the art.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy disclosed by Pivac et al. as an initial therapy and/or to administer it as soon as possible. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Pivac et al. and Merck already **disclose** the treatment to be useful as a treatment for depression generally, and because it is standard practice in the art to administer a therapy promptly **once it is indicated**. One of ordinary skill in the art would reasonably have expected success because choosing a particular therapeutic regimen from among the various options available in the prior art is within the routine and ordinary level of skill in the art. Finally, it would have been **obvious** to one of ordinary skill in the art to administer the antipsychotic in a **low** dose. One of ordinary skill in the art would have been motivated to administer the lowest effective dose

of the drug because of the well known side effects of typical antipsychotic drugs. One of ordinary skill in the art would have reasonably been able to adjust the dosage of the compounds administered to achieve the optimal result while minimizing toxicity from the drugs themselves. Thus the invention taken as a whole is *prima facie* obvious.

#IX of third reply (first reply after RCE): (see also #III as for initial therapy etc, and for "once indicated")and for low dose.
The PTO said: "Claims 1,2,4,5,6, 10-14, 16-18, 20-22, 24-26, 28-30, 32-38, 41-43, 48,49,51-64,66,70-77,79-81,83-85,87-89,91-105,109-122, and 124-129 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pivac et al."

My reply:
- PTO stated that "Pivac et al. discloses that atypical antipsychotics ... should be coadministered with selective serotonin reuptake inhibitors, because they produce a synergistic effect. (p. 236, left column, last paragraph, right column first paragraph)."

However,

#IX / **1)** Please note that In re Donohue, 766 F.2d 531 [Fed. Cir.1985]. "A patent or printed publication is an insufficient disclosure if it is not enabling." "The examiner cannot use references as prior art if such references have insufficient disclosures."
However, **even if** Pivac would have not just merely mentioning a synergestic effect **without enabling it,** that reference would still not anticipate or make our invention obvious:

#IX / **2)** The Ferris reference needs also be taken into consideration. (**Ferris R.M. et al Buproprion: A new antidepressant drug, the mechanism of action of which is not associated with down-regulation of postsynaptic β-adrenergic, serotoninergic (5-HT-2), α2-adrenergic, imipramine and dopaminergic receptors in brain. Neuropharmacology 1983 22, No 11 pp 1257-1267.** – copy enclosed). Since as per Ferris buproprion failed to alter the sensitivity of other receptors that had been implicated in the mechanism of action of other antidepressant drugs (i.e. **5-HT2**) (page 1266 lines 30-34, **5-HT1** (page 1260 Results section lines 6-8) and since Ferris (at page 1266 lines 41-44=last four lines) concluded that on these results that "the concepts concerning the biochemical altercations involved in depression [that is including Pivac's and Jordan's theoretical assumption and the role of 5-HT2 and 5-HT1 receptors] and how antidepressant treatment affects these parameters **should be re-evaluated**". Therefore, the PTO's argument that the Pivac (and/or Jordan) references would be rendering our invention obvious is not convincing. Therefore the rejection must be withdrawn.

#IX / **3)** This is independent from the above argument. It had been conceptualized as also referenced in the above Ferris reference (page 1257 summary lines 13-14) that down-regulation of

CNS receptors had been commonly implicated in the mechanism of action of antidepressant drugs. **Kuoppamaki M. at al (Differential regulation of rat 5-HT2A and 5-HT2C receptors after chronic treatment with clozapine, chlorpromazine and three putative atypical antipsychotic drugs Neuropsychopharmacology 13:139-150, 1995)** showed that while risperidone had affinity to 5-HT2A receptors, chronic treatment with risperidone had no significant effect on 5-HT2A receptor binding (see page 144 last two lines of second column). Kuoppamaki had concluded that "**it may be that also other properties** ... than high 5-HT2A receptor occupancy **are needed** to elicit down-regulation of 5-HT2A receptors (p 147 first column lines 32-36.). Thus Pivac's simple statement that atypical antipsychotics have affinity to the 5-HT2A receptors would not explain in light of Ferris and Kuoppamaki of explaining of how antipsychotics would augment the effects of SSRIs or of how the theory of down-regulation of CNS receptors that had been commonly implicated in the mechanism of action of antidepressant drugs would fit in with these results. Therefore the PTO's argument that the Pivac reference would be rendering our invention obvious is not convincing. Therefore the rejection must be withdrawn.

#IX / 4) Confounding the theory in regards to the role of 5-HT2A receptors, and making any conclusions difficult on the agents acting on 5-HT2A receptors is the sharp contrast of in vitro and in vivo studies on the 5-HT2A receptor mRNA levels. While **Toth M et al (Antagonist-mediated down-regulation of 5-hydroxytryptamine type 2 receptor gene expression: modulation of transcription Molecular Pharmacology 45:11095-1100, 1994)** have demonstrated in vitro that mianserin has down-regulated the 5-HT2A receptor mRNA (page 1098 second column second paragraph's first two lines), an in vivo study by **Roth BL et al (chronic mianserin treatment decreses 5-HT2 receptor binding without altering 5-HT2 receptor mRNA levels European Journal of Pharmacology – Molecular Pharmacology Section, 207 (1991) 169-172)** had shown that mianserin did not alter the receptor mRNA level (p 171 second column last paragraph). Therefore the PTO's argument that the Pivac reference would be rendering our invention obvious is not convincing. Therefore the rejection must be withdrawn.

#IX / 5) At the Pivac reference the synergestic effect of M100907 and fluoxetine is explained "because of 5-HT(1A) autoreceptor blocade" (page 236 of Pivac first column "a new combination" line 4-7). At the same page of this article (p 236 second column line 7-9) they explain that pindolol as 5-HT 1A antagonist can also potentiate the effects of SSRIs. Now that raises grounds for opposition both clinically, and from patent prosecution standpoint in various ways.

#IX / 5-A) Prior art reference (Cremers) showed that pindolol's blockade of presynaptic 5-HT(1A) autoreceptors does **not** augment the SSRI-induced 5-HT increase in the guinea pig brain. "Therefore very unlikely that the favorable effects of combining pindolol with SSRIs, as reportefirst second paragraph lines 1-3) **(Cremers TI, et al Is the beneficial antidepressant effect of coadministration of pindolol really due to somatodendritic autoreceptor antagonism? Biol Psychiatry 2001 Jul 1; 50(1):13-21. – enclosed).**

Therefore, PTO did not show evidence in prior art - in particular "in view of Merk" - that the atypical antipsychotics, would show more or less blockade of the presynaptic 5-HT(1A) autoreceptors than pindolol which did not augment the SSRI-induced 5-HT increase and was found to be very unlikely that the favorable effects of combining pindolol with SSRIs would be indeed due

to 5-HT(1A) antagonism. In particular, the PTO has failed to show that to each and every atypical antipsychotic medications. Therefore the PTO's line of reasoning is not convincing and the rejection should be withdrawn.

#IX / 5-B)

Moreover, another reference by the PTO the Jordan reference (WO 02/060423) at page 2 lines 22-24 specifically refers to the compound in that invention (see page 15 circled by the PTO as aripriprazole) was enabled of having agonistic activity (not blockade) on the 5-HT1A receptor subtype compared to their reference compound. [At page 4 lines 8-9 they also reference buspirone having also 5HT1A receptor agonist activity of which we will refer later see #X below].

Therefore, the PTO did not show a convincing line of reasoning, or prior art evidence that if the atypical antipsychotics, would show more or less blockade of the presynaptic 5-HT(1A) autoreceptors than pindolol, and therefore in view of **Cremers** (above) if they also would or would not likely explain favorable effects of combining these substances with SSRIs and that the effect are due to 5-HT(1A) antagonism. Also in view of Cremers it is also not clear that what degree of 5-HT(1A) antagonism would be necessary for a drug to sufficiently augment the SSRI induced 5-HT increase (since the effect of pindolol was unlikely carried out through such explanation). Therefore the PTO's line of reasoning is not convincing and the rejection should be withdrawn.

#IX / 5-C) In addition, as we have discussed in the PTO mentioned **Pivac reference the synergestic effect of M100907 and fluoxetine is explained "because of** 5-HT(1A) autoreceptor blocade" (page 236 of Pivac first column "a new combination" line 4-7). At the same page of this article (p 236 second column line 7-9) they explain that pindolol as 5-HT 1A antagonist can also potentiate the effects of SSRIs. (p 236 second column line 7-9) they explain that pindolol through the same 5-HT 1A antagonist mechanism. However, it was shown that augmentation of antidepressant effect (for treatment resistant depression) by pindolol was no more effective than placebo. **(Perez V et al A double-bind, randomized, placebo-controlled trial of pindolol augmentation in depressive patients resistant to serotonin reuptake inhibitors. Arch Gen Psychiatry. 1999; 56(4):375-379**. -included). Therefore, in view of **Perez and Pivac** that attempt through such molecular explanation and similarity with pindolol would not be enabling and would not make our invention obvious. Therefore the PTO's line of reasoning is not convincing and the rejection should be withdrawn.

#IX / 6-a) Another ground for opposition is clinical. **Even if** the PTO would sufficiently answer to all of the above; the clinical risk benefit analysis a new and inventive step to apply our invention as initial treatment; for the (non-inherent) claimed purposes and for substantially all or all patients (within the claimed group) would be still not proven in the prior art. The use for cognitive distortions would also not proven in the prior art. (See (#III, and #IX/ 7) to #IX/ 11) below). Therefore all what we have said (#III, and above in #IX); as well as in #III/13, under the history of clozapine and how it had a (new) patent term – because of the new inventive steps - for 37 years would be also applicable here. Just because an agent (like clozapine, or in our case the atypical antipsychotics) would be known to treat a disorder, that does not necessarily enable the clinicians to apply these agents for a subgroup of that disorder.

#IX / 6-b) In addition if another non-antipsychotic agent, either pindolol or one like pindolol would have a similar receptor profile (to both pindolol and the atypical antipsychotics – as that similarity on 5-HT1A receptor is claimed by the Pivac reference which was cited by the PTO), and if indeed these agents would have the same efficacy, than that non-antipsychotic agent with less side effect (no NMS no TD) would be considered first to the antipsychotics according to the risk/benefit alternatives at the time of our invention and according to the same receptor profile as claimed by Pivac. Therefore it would not be obvious to use the antipsychotic over pindolol. The risk/benefit/side effect analysis cannot be left out.
(We on the other hand also gave guidance in our utility that the combination of an antidepressant with an antipsychotic is likely be superior to another augmentation strategies like two antidepressants. (See page 14 lines 9-12). [However, the non-antipsychotic agent simply based on the 5-HT1A receptor profile would not decrease cognitive distortion or likely would not be as effective in decreasing SI.]

[As we have shown above the speculation on the blockade of presynaptic 5-HT(1A) autoreceptors (see **Cremers**) does not stands firm, and would not make our invention obvious. The apparent lack of enablement in the cited reference(s) (Pivac) or unconfirmed speculation based on the blockade of presynaptic 5-HT(1A) autoreceptors does not stands firm (**Cremers**). However, that would not jeopardize the enablement of our invention, as we enabled our compound and the medication combination through a different mechanism(s). This is specifically true for the effect on cognitive distortion and for the decrease of suicide rates.]

#IX / 7) Under #III above we have addressed of why the initial treatment, and also the low dose would not be obvious; and that reply would be also applicable here. Therefore the rejection should be withdrawn for the same reasons.

#IX / 8) We have discussed above [#III 14a)-14f)] of why the cited uses in our claims are not inherent. These claims therefore would be (also) allowable.

#IX / 9) Even if for any unforeseen and other than above mentioned reasons by the PTO our invention would be rejected; our invention should still be accepted based on our invention targeting cognitive distortions. (see #III above) However as our reply shows the PTO's rejection as presented should be withdrawn, as it did not present a convincing line of evidence.

#IX / 10) The PTO has disregarded the vast amount of secondary factors (not just the mere passage of time) (as it was also brought up e.g. under #III above) in support of my invention. (RCE pp 32-34 2nd reply #11); January 17,2007 Amendment pp 93-99 and its enclosures).

#IX / 11) Anticipation by Pivac could not occur also (based on the new risk/benefit analysis) as neither Pivac nor the PTO recognized the value of and need to apply our method for substantially all and all patients (within our claims). Even though – as the PTO referencing us – we use a may and no a must use our method, from our specification it becomes clear that **a)** the risk/benefit analysis needs to be discussed with the patient, **b)** that patient right issues would not allow to use our

method against the will of the patient, **c)** and that the skilled in the art must also look the benefit of the group [since we do not know who in the group would be affected – e.g. by suicide – as it was explicitly described with the analogy of how we were treating appendicitis]. **d)** Our specification also drew attention to the discrepancy that in prior art no one paid attention that if the patient (with personality disorder) bothers the psychiatrist than we psychiatrists gave them multiple of psychotropic medications [sometimes 4 or 5 of them at the same time], but if the patient with depression with much higher risk of suicide die quietly nobody seems to be bothered and our field hides under the risks and side effects of the antipsychotics of why these cannot be used. This is unacceptable, and that was one of our reasons and one of our clinical guidance for enablement. It is therefore understood that really our method is (also) for substantially all and all patients as an initial treatment (within our diagnostic category). This was nowhere anticipated by Pivac either.
(For the above and for the discrepancy in the statistics of the suicide between the two patient group please also refer to our specification). (See parts re-entered with RCE to our specification page 112 fourth paragraph).

[See also clozapine example under #III 13) for the value of the new risk/benefit analysis; and #III/13b-3d) last 3 paragraphs and #III/10.]

From page 28

Claims 1-4,7,8,10-15,19,23,27,31,36-38,41-43,48,49,51-63, 67, 68, 7074,78,82,86,90,95-105,109-122, and 124-130 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jordan et al: (PCT international publication W002/060423, reference included with PTO-892) in view of Merck. (Reference included with PTO-892) Jordan et al. discloses a method of treating a patient suffering from a disorder of the central nervous system associated with the 5-HT1A receptor, comprising administering a compound having a given structure. (p. 15, lines 5-18) According to the Chemical Abstracts Registry entry 129722-12-9, (reference included with PTO-892) this structure is aripiprazole. This compound is useful for treating various disorders of the central nervous system, for example **major depression** and melancholia, as well as various **cognitive distortions including obsessive compulsive disorder, alcohol and drug addiction,** and cognitive impairment. (p. 16, line 23 -p. 17,

line 10) The preferred unit dosage form is 1-20 mg of active agent. (p. 18, lines 5-10) Jordan et al. does not disclose a method comprising administering aripiprazole in combination with an antidepressant. Jordan et al. does not explicitly disclose a method of administering the claimed treatments as an initial treatment, as soon as possible, or upon presentation to a physician or other health care provider, or a method comprising administering 2.5-15 mg of aripiprazole.

Merck discloses a list of antidepressants useful for treating major depressive disorder. (p. 1534, table 189-6) These antidepressants include various antidepressants recited in the instant claims such as Clomipramine, fluoxetine, sertaline, paroxetine, and fluvoxamine.

It would have been obvious to one of ordinary skill in the art at the time of the invention to **co-administer the antidepressants** of Merck with the typical antipsychotics of Jordan et al. to a patient suffering from major depression either alone or **complicated by any of the various cognitive distortions** recited by Jordan et al. One of ordinary skill in the art would have recognized that these two therapies can be combined because they are both directed toward treating the same condition, namely major depressive disorder. **Combining two known prior art therapies is well within the ordinary and routine level** of skill in the art.

It would have been **obvious** to one of ordinary skill in the art at the time of the invention to administer the therapy disclosed by Jordan et al. as an **initial therapy** and/or to administer it as soon as possible. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Jordan et al. and Merck already disclose the treatment to be useful as a treatment for depression generally, and because it is standard practice in the art to administer a therapy promptly **once it is indicated**. One of ordinary skill in the art would reasonably have expected success

because choosing a particular therapeutic regimen from among the various options available in the prior art is within the routine and ordinary level of skill in the art.

It would also have been **obvious** to one of ordinary skill in the art at the time of the invention to practice the method of Jordan et al. using a dose of 2.5-15 mg of aripiprazole per day. One of ordinary skill in the art would have been motivated to use this rang, and would have reasonably expected success in doing so, because the range disclosed by Jordan et al. significantly overlaps with the range of the claimed invention, which is considered to represent Applicant's low dose regimen. When the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. See *In re Wertheim,* 541 F.2d 257,191 USPQ 90 (CCPA 1976); *In re Woodruff,* 919 F.2d 1575,16 USPQ2d 1934 (Fed. Cir. 1990). See MPEP § 2144.05 [R-1].

Thus the invention taken as a whole is *prima facie* obvious.

#X of third reply (first reply after RCE): (see also #III cog distortion, initial treatment "as indicated") [and in view of...]

PTO said: Claims 1-4,7,8,10-15,19,23,27,31,36-38,41-43,48,49,51-63, 67, 68, 70-74,78,82,86,90,95-105,109-122, and 124-130 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jordan et al. in view of Merck.

My reply:

#X / 1) The Ferris reference needs also be taken into consideration. (**Ferris R.M. et al Buproprion: A new antidepressant drug, the mechanism of action of which is not associated with down-regulation of postsynaptic β-adrenergic, serotoninergic (5-HT-2), α2-adrenergic, imipramine and dopaminergic receptors in brain. Neuropharmacology 1983 22, No 11 pp 1257-1267**. – copy enclosed). Since as per Ferris buproprion failed to alter the sensitivity of other receptors that had been implicated in the mechanism of action of other antidepressant drugs (i.e. 5-HT2) (page 1266 lines 30-34, **5-HT1** **(page 1260 Results section lines 6-8)** and since Ferris (at page 1266 lines 41-44=last four lines) concluded that on these results that "the concepts concerning the biochemical altercations involved in depression and how antidepressant treatment affects these parameters should be re-evaluated" the PTO's argument that the Pivac (and/or Jordan) references would be rendering our invention obvious is not convincing. Therefore the rejection must be

withdrawn.

In addition, since an interaction occurs between 5-HT1 and 5-HT2 receptors at the individual neuronal level, all what we have said under #IX also stands here (as requirements to get answer to for anticipation of our claims).
It is also of note that it was described that the serotoninergic neurons have intrinsic tonic pacemaker activity.

Furthermore, what is clouding the issue to make conclusions from the receptor binding or affinity level (as the only source of "enabling" and information) on the clinical effect of a drug is that it was described that in contrast to the classical theory that described that certain cells possess only a single neurotransmitter transmission (or receptor) was found to be incorrect. In addition, according to the so called "agonist directed trafficking", single receptors interacting with multiple pathways may result in that the pattern of intracellular signaling may differ depending on the agonist. So simply from a receptor binding or affinity (as [under #IX and #X] the cited references and examples also attest to that confusion) the PTO cannot assume anticipation that a clinician (skilled in the art) with that knowledge would go ahead with these uncertainties and give these (experimental) drugs to a patient without sound clinical reason and without undue experimentation. It is of note that aripriprazole was not FDA approved at the time of our priority date, at the time of the submission of our provisional application to the best of my recollection. In short anticipation and obviousness could not occur from the Jordan (or Pivac) references as the other numbered sections also point that out.

#X / 2a-1) At page 2 (lines 22-24) the Jordan reference states that it has not been reported before that compounds in the present invention / arippriprazole, have agonistic activity at 5-HT1A receptor subtype. Their enablement is restricted to showing that activity of their test compound with a reference compound. (page 18). At page 4 they refer to a WO reference disclosing "5HT1A receptor agonist, buspirone". The Jordan reference does not enables aripriprazole in clinical trials (or in any other ways) of being efficacious for the treatment of depression that they claim (e.g their claim 2, 21, 22; [and in claims 19, 21 drug addiction]. Jordan specifically does not enable aripriprazole for initial treatment or for our other claims. The sole enablement is based on, having agonistic activity at 5-HT1A receptor subtype **just like** the compound **buspirone** that was cited by them:

#X / 2a-2) It is therefore notable that buspirone is not approved by the FDA for the treatment of depression. In fact buspirone is also **not** used off label for the treatment of depression. While some open studies initially suggested efficacy for buspirone for an augmentation strategy with SSRIs a controlled study available at the time of our invention did not support that use, yielded negative result, and was not more efficacious than placebo. **(see enclosure. M. Landen et al A randomized, double-blind, placebo-controlled trial of buspirone in combination with an SSRI in patients with treatment-refractory depression. J. Clin Psychiatry 1998; 59:664-668.)**
At minimum, in view of Landen, the uncertainty on the effectiveness of buspirone to augment treatment resistant depression needs to be acknowledged.

Therefore in view of the above, at the time of our invention the average skilled in the art based on the Jordan publication could not anticipate our invention. The sole enablement of Jordan is based

on, having agonistic activity at 5-HT1A receptor subtype just like the compound buspirone. Buspirone is not approved by the FDA for the treatment of depression.
The Jordan reference specifically does not enable initial treatment or the other usage of our claims. Therefore the PTO did not present a convincing line of reasoning and the **rejection should be withdrawn**.

#X / 3) Even if we further analyze the Jordan reference we cannot find enablement.
In the Jordan reference aripriprazole was being described as having agonistic activity at 5-HT1A receptor subtype (page 2), while buspirone being 5-HT1A receptor agonist (page 4 line 8-9) and buspirone being 5-HT1A partial agonist (page 4 lines18-19).
The Jordan reference (page 4) makes a reference that another agent gepirone (being 5-HT1A partial agonist) (page 4 lines 25-), **not** quite sharing the same receptor profile as aripriprazole. Note that their test compound was described as having agonistic activity at 5-HT1A receptor (and at page 22 demonstrating high affinity binding to H5-HT1A receptors). They note that another agent gepirone (being 5-HT1A partial agonist) can be combined with an antidepressant to effectively treat depression. That was in the context that this two compound not quite sharing receptor profiles. (Jordan reference (page 4) as above).

However, even if the disclosed gepirone and aripriprazole would share the same receptor profile, the following fact was known in the art that two serotoninergic antidepressants can be combined to treat treatment resistant depression. That however does not make our claims obvious. (See #IX 5-c) above). The enablement of the Jordan reference is done simply by having agonistic activity at 5-HT1A receptor, however that does not give enablement to our claims.

In our specification / or response we described if safer (non-antipsychotic 5-HT would be available that should be used over an antipsychotic secondary to risk/benefit/side effect analysis profile. We specifically highlighted the antipsychotic's role (e. g. overlap with cognitive distortion and effect on depression thought cognitive distortion, that buspirone or gepirone would not effect. Therefore the 2 compounds are not replaceable simply on basis of 5-HT(1A) activity, or for our reasons (effectiveness) to "prevent" SI.

Therefore the Jordan reference does not anticipate or enable or our other claims.

#X / 4) In addition the Jordan reference specifically does not enable or even mention initial treatment and our other claims.
Under #III above we have addressed of why the initial treatment, would not be obvious; and that reply would be also applicable here. Therefore the rejection should be withdrawn for the same reasons.

#X / 5) We have discussed above [#III 14a)-14f)] of why the cited uses in our claims are not inherent. These claims therefore would be (also) allowable.

#X / 6) It is notable that the PTO again equals various medical conditions with cognitive distortions without giving any prior art evidence for that. Cognitive impairment does not equal of

cognitive distortions as thought or defined by prior art. Cognitive distortions may be found in various medical conditions but that does not make them equal to cognitive distortions. (We have discussed that under #III above, and all of what was said there is also applicable here). (As regards to addiction there is a vast amount of literature for brain changes and receptor changes, and molecular mechanisms for craving, and that is different and cannot be equaled to cognitive distortion). There is no single prior art reference, or a convincing line of reasoning by the PTO suggesting that at the time of our invention the ordinary skilled in the art would have known that the medications in our claims would be effective for and would target cognitive distortions. There is not even a single (or more) reference cited by the PTO showing enablement for such claims.

Therefore, even if for any unforeseen and other than above mentioned reasons by the PTO our invention would be rejected; our invention should still be accepted based on our invention targeting cognitive distortions. (see #III above) However as our reply shows the PTO's rejection as presented should be withdrawn, as it did not present a convincing line of reasoning.

#X / 7) The PTO has disregarded the vast amount of secondary factors – not just the mere passage of time (as it was also brought up e.g. under #III above) in support of my invention. (RCE pp 32-34 2nd reply #11); January 17,2007 Amendment pp 93-99 and its enclosures).

#X / 8) Anticipation by Jordan could not occur also (based on the new risk/benefit analysis) as neither Jordan nor the PTO recognized the value of and need to apply our method for substantially all and all patients (within our claims). Even though – as the PTO referencing us – we use a may and no a must use our method, from our specification it becomes clear that **a)** the risk/benefit analysis needs to be discussed with the patient, **b)** that patient right issues would not allow to use our method against the will of the patient, **c)** and that the skilled in the art must also look the benefit of the group [since we do not know who in the group would be affected – e.g. by suicide – as it was explicitly described with the analogy of how we were treating appendicitis]. **d)** Our specification also drew attention to the discrepancy that in prior art no one paid attention that if the patient (with personality disorder) bothers the psychiatrist than we psychiatrists gave them multiple of psychotropic medications [sometimes 4 or 5 of them at the same time], but if the patient with depression with much higher risk of suicide die quietly nobody seems to be bothered and our field hides under the risks and side effects of the antipsychotics of why these cannot be used. This is unacceptable, and that was one of our reasons and one of our clinical guidance for enablement. It is therefore understood that really our method is (also) for substantially all and all patients as an initial treatment (within our diagnostic category). This was nowhere anticipated by Jordan either.
(For the above and for the discrepancy in the statistics of the suicide between the two patient group please also refer to our specification). (See parts re-entered with RCE to our specification page 112 fourth paragraph).

[See also clozapine example under #III 13) for the value of the new risk/benefit analysis; and #III/13b-3d) last 3 paragraphs and #III/10.]

#X / 9) The question of the low dose in regards to the Jordan reference is irrelevant since the Jordan reference was not enabling our claims at any dose.
We have shown that the patentability of our claims exists, and our preferred specification for a low dose regimen with it is maintained.

From page 30

Claims 106-108 are rejected under 35 U.S.C. 103(a) as being unpatentable **over Jordan** et al. (Reference of record in PTO-892) **in view of Berman** et al. (Reference of record in previous action) The disclosure of Jordan et al. is discussed above. Jordan et al. does not disclose a method in which the antidepressant is ketamine.

Berman et al. discloses that ketamine exerts antidepressant effects in human patients. (p. 351, second paragraph, right column, p. 352, left column, last paragraph, p. 353, right column, first paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to use ketamine as an antidepressant in combination with a typical antipsychotic recited in the method of Jordan et al. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Berman et al. reveals that ketamine is useful for the same purposes as the therapies recited by Jordan et al., namely treating depression. One of ordinary skill in the art would reasonably have expected success because ketamine is already known to be useful as an antidepressant.
Thus the invention taken as a whole is *prima facie* obvious.

#XI of third reply (first reply after RCE): (see also #X , III)
The PTO said: Claims 106-108 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jordan et al. (Reference of record in PTO-892) in view of Berman et al.

My reply:

#XI / 1) It is notable that The PTO errs as Jordan reciting antipsychotics in combination with their test compound (aripriparziole) was listed for the treatment of resistant schizophrenia and not for depression in their claims e.g. claims 4, 6, 3, 7-15, and 25-29.

#XI / 2) Since under **#X** above we have successfully and sufficiently argued that our invention is patentable over Jordan, the conclusion of "Thus the invention taken as a whole is *prima facie* obvious" is also incorrect. Therefore the rejection should be removed.

(Please also refer to #IV, and #VII, above also pertaining in view of Berman and Reply 1 and Reply2 – RCE that are also explicitly incorporated herein also in regards to what we have said about ketamine).

From page 31

Claims 3-5, 9-15,20,28,37, and 50-52 are rejected under 35 U.S.C. 103(a) as being unpatentable **over Theobald** et al. (US patent publication 2003/0049308, first published as PCT international publication W001/80837) Theobald et al. discloses a transdermal or transmucosal patch comprising nicotine and a further active substance, that is useful for treating nicotine dependency, for nicotine substitution, or for disaccustoming smokers. (p. 1, paragraphs 0002, 0003, and 0009) The additional active agent can include antidepressants **or** neuroleptics (antipsychotics), for example chlorpromazine, perphenazine, sulpride, clozapine, clomipramine, doxepin, risperidone, paroxetine, or f1uvoxamine. (p. 2, paragraphs 0015-0017) Theobald et al. does not explicitly exemplify a method comprising administering said patch comprising nicotine, an antidepressant, and an antipsychotic.

It would have been **obvious** to one of ordinary skill in the art at the time of the invention to practice the method of Theobald et al. using nicotine in combination with **both** an **antidepressant and an antipsychotic**. One of ordinary skill in the art would have been motivated to practice the invention in this manner **because each of the additional agents (the antidepressant and the antipsychotic) is revealed individually by Theobald** et al. **to be useful in combination with nicotine** for the treatment of nicotine addiction. **Adding both** of these agents at once to the

disclosed invention is well within the ordinary and routine level of skill in the art and carries a reasonable expectation of success in achieving the desired therapeutic goal. .

Thus the invention taken as a whole is *prima facie* obvious.

#XII of third reply (first reply after RCE):
The PTO said: Claims 3-5, 9-15,20,28,37, and 50-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Theobald et al. (US patent publication 2003/0049308, first published as PCT international publication W001/80837) Theobald et al. discloses a transdermal or transmucosal patch comprising nicotine and a further active substance, that is useful for treating nicotine dependency.

My reply:

#XII / 1) It is of note that the PTO did not enclose in the office action the Theobald reference. Therefore the rejection may be improper.

#XII / 2) It seems that the Theobald reference is on the technique of how to administer medicaments with transdermal or transmucosal patch comprising nicotine and a further active substance. The PTO did not show that where would the Theobald publication give any reference on the whereabouts of the publication in the literature or prior art, that both antidepressants and the antipsychotic medications either alone or in combination would have been adequately proven to be useful in the treatment of nicotine addiction, nicotine withdrawal or smoking cessation. In absence of that the Theobald reference is not enabling. (The PTO alternatively can also show that the Theobald publication had studies proving the effectiveness of antipsychotics and antidepressants or enabling our method in their written description any other way).
Therefore the Theobald reference is **not enabling** for the purposes of our claims.

"The examiner cannot use references as prior art if such references have insufficient disclosures." In re Donohue, 766 F.2d 531 [Fed. Cir.1985]. "A disclosure is non-enabling if it fails to place the subject matter of the claims within the possession of the public..." (page 60 lines 35-42) - As cited in our prior reply/RCE (page 17).

In addition, the PTO did not "present a convincing line of reasoning as to why the artisan would have found [our] claimed invention to have been obvious in light of the teachings of the references", **and the rejection needs to be withdrawn.** (Ex part Clapp, 227 U.S.P.Q. 972 (Bd. Pat App. & Inter. 1985)." (Rogers JL The Complete Patent BookSphinx Publishing Napervile, IL 2003 page 219).

#XII / 3) Our method would still be patentable as a novel non-obvious invention through our enablement of our method to treat cognitive distortions.
(We have discussed under #III 2a) -2f) the reasons of why the PTO's reasoning was not convincing and removing rejection in regards to cognitive distortions.

Claims discussion:

Summary of the reply to the Claim Objections

Claims 1-9,11-12,37,38,41-43,48-50,53-71,95-103, and 126 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating depression, cognitive distortions, smoking cessation, or nicotine withdrawal comprising administering certain antidepressants defined in the specification and prior art, does not reasonably provide enablement for such a method involving any antidepressant whatsoever.

#I of third reply (first reply after RCE):
We will overcome this objection by amending claims 1-3. We would also add new claims 131-139. (and 140-143) **to comply with overcoming the PTO's objection.**

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Claim 65 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. claim 65 has been fully considered and but is deemed to insert new mater.

#II of third reply (first reply after RCE):
We describe why it is an inherent step.

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Claims 1-4, 6,10-15, 18,22,26,30,36-38,41-43,48,49,51-63,66,70-74,77, 81,85,89,95-105,109-122,124, and 126-130 are rejected under 35 U.S.C. 103(a) as being obvious over Chappell

#III of third reply (first reply after RCE):
It is discussed **view of Kramer** that the D4 antagonism does not prove antipsychotic activity.
We are also discussing among others of why anxiety and cognitive distortions are not interchangeable among **others in view of Spilberger, Barlow, Goldapple, Brody, Sharp, Azhar, DeRubeis references**.
We discuss why it not had been obvious for the ordinary in the art to administer the therapy disclosed by Chappell as initial treatment.
We discuss how off-label administration of medications can be used by the clinicians.
We discuss that It was left out that if the differences in doses are crucial the invention is patentable.
We discuss that a mere statement by Chappell to use his invention for a larger group without enablement is not sufficient disclosure and would not enable the ordinary skilled in the art to use Chappell's method for our claims, and that why the PTO's reasoning that the artisan would skip clinical steps was unconvincing.
We discuss that introducing a new risk/benefit analysis which (along with other guidance) enables new methods to save lives at large scale is a surprising new discovery. The secondary factors also support to that fact.
We discuss of **how a new risk/benefit/side effect analysis as exemplified by Clozaril (clozapine) was a new step protectable by intellectual property laws** with new patents for clozapine extendeing its' monopoly for 37 years after the discovery of this drug.
We discuss of why the intended uses recited in the instant claims, were not inherently present. This is also discussed **in view of Simon**, as also exemplified by the secondary factors (much more than the mere passage of time) that we have presented in our prior replies.

-
Claims 106-108 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chappell et al. (US patent application 10/001827, Pub. Number 2002/0094986 A 1, of record in previous office action) in view of Berman

#IV of third reply (first reply after RCE):
We have sufficiently answered that our claims would be patentable over Chappell, and so it would also be in view of Berman, removing this rejection.

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new grounds of rejection are introduced:
Claims 126-128 are rejected under 35 U.S.C. 102(b) as being anticipated by Robertson (cognitive distortion).

#V of third reply (first reply after RCE):
That was in part answered under #III 2a) to 2f) above).
We have also discussed of why anticipation could not occur for the skilled in the art for the purpose of our claims on relying on the Robertson reference.
-

Claim Rejections -35 USC § 103
basis for all obviousness
Claims 5, 16, 17,20,21,24,25,28,29,32-35,64,75,76,79,80,83,84,87,88, 91-94, 123, and 125 are rejected under 35 U.S.C. 103(a) as being unpatentable **over Chappell** as applied to claims 1-4,6,10-15,18,22,26,30,36-38, 41-43,48,49,51-63,66,70-74,77,81,85,89,95-105, and 109-122,124, and 126-30 above, and further in view of Schmidt

#VI of third reply (first reply after RCE):
Since under **#III** above we have sufficiently answered that our invention is patentable over Chappell particularly **in view of Kramer,** therefore we have removed the rejection.
-

Claims 5, 9, 16, 20, 24, 28, 64, 75, 79, 83, 87, and 125 are rejected under 35 U.S.C. 103(a) as being unpatentable **over Chappell** as applied to claims 1-4,6,10-15,18,22,26,30,36-38,41-43,48,49,51-63, 66,70-74, 77,81,85,89,95-105, and 109-122, 124, and 126-30 above, and further in view of Roth

#VI of third reply (first reply after RCE):
Since under **#III** above we have sufficiently answered that our invention is patentable over Chappell particularly **in view of Kramer,** therefore we have removed the rejection.

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Claims 1-3, 9,11-15,37,38,41-43,48,49,53-62,69-74,96-105, and 129 are rejected under 35 U.S.C. 103(a) as being unpatentable **over Robertson** as applied to claims 126-128 above, and further in view of the Merck Manual

#VII of third reply (first reply after RCE):

We have also discussed of why anticipation could not occur for the skilled in the art for the purpose of our claims on relying on the Robertson reference.

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Claims 106-107 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robertson et al. (Reference of record in PTO-892) in view of Berman

#VIII of third reply (first reply after RCE):
Since under # VII we have also discussed of why anticipation could not occur for the skilled in the art for the purpose of our claims on relying on the Robertson reference, that is also true in view of Berman.

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Claims 1,2,4,5,6, 10-14, 16-18, 20-22, 24-26, 28-30, 32-38, 41-43, 48,49,51-64,66,70-77,79-81,83-85,87-89,91-105,109-122, and 124-129 are rejected under 35 U.S.C. 103(a) as being unpatentable **over Pivac**

#IX of third reply (first reply after RCE):
This was discussed among others in view of the **Ferris, Kuoppamaki, Toth, Roth, Cremers, and Perez** references in addition to of why the initial treatment, and also the low dose would not be obvious.

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Claims 1-4,7,8,10-15,19,23,27,31,36-38,41-43,48,49,51-63, 67, 68, 7074,78,82,86,90,95-105,109-122, and 124-130 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jordan in view of Merck

#X of third reply (first reply after RCE):
This was discussed among others in view of the **Ferris, Landen** references in addition to of why the initial treatment would not be obvious.
This was further discussed in analyzing the Jordan reference.
We have also discussed of why the cited uses in our claims are not inherent.

-
Claims 106-108 are rejected under 35 U.S.C. 103(a) as being unpatentable **over Jordan** et al. (Reference of record in PTO-892) **in view of Berman**

#XI of third reply (first reply after RCE):
Since under #X we have discussed of why anticipation could not occur for the skilled in the art for the purpose of our claims on relying on the Jordan reference, that is also true in view of Berman.

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Claims 3-5, 9-15,20,28,37, and 50-52 are rejected under 35 U.S.C. 103(a) as being unpatentable **over Theobald**

#XII of third reply (first reply after RCE):
The PTO did not enclose in the office action the Theobald reference. Therefore the rejection may be improper.
The PTO did not show that where would the Theobald publication give any reference on the whereabouts of the publication in the literature or prior art, that both antidepressants and the antipsychotic medications either alone or in combination would have been adequately proven to be useful in the treatment of nicotine addiction, nicotine withdrawal or smoking cessation. In absence of that the Theobald reference is not enabling.
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Replies # I-XII should sufficiently address the withdrawal of claims.

Claims, 1-3, 36, 54, 57, 95, 108, 122,123,130, are currently amended.

New claims 131-139 and 140143 are presented and are discussed under separate heading.

Additional remarks

It is important to note that suicide takes about 30.000 lives in the US alone resembling the death rate from leukemia. In five years it is up to 150.000 lives in the US alone that could have been saved – which is almost about half of the fatality of the worst (contagious) infectious epidemic in the US ever (the 1918 flu epidemic) – even though the effectiveness of our method may not be 100%. The PTO cannot assume that if our invention would have been obvious in light of the prior art than the secondary factors would so drastically contradict to the PTO's assumption 5 years later. In discussing the secondary factors in the 1st reply we also made reference of the potential and likely legal liabilities form "big pharma" and the FDA of not coming forward to the media with such an important discovery. We also mentioned the financial incentives for "big pharma" in the range of billion(s) of dollars a year. The PTO did not address our arguments about the secondary factor, and did not even acknowledge the existence of that section.

We respectfully request the allowance of our amended claims.

Discussion of the new claims:

New Claims 131-133 had been introduced to overcome the PTO's "any antidepressant" objection and still present a broader claims than the now amended claim 1-3. The language for these new claims had been taken from the reintroduced specification in the RCE page 121 second paragraph lines 17-20.

New Claims 134-139 are independent from Claims 131-133 and the format is similar to the previously presented claims. Since New Claims 131-133 present a broader coverage, they are not duplicate claims.

New Claims 140 -143 are introduced from the specification and are related the either the new risk/benefit analysis or to the intended use (Claim 142). To show the PTO that where the language of these claims came form, (and therefore to see that these new claims to the applicant's best knowledge does not contains new matter) please see copy of the specifications reintroduced specification in the RCE with the language that had been contemplated in the claims highlighted in bold. (When the applicant crafted the claims he highlighted these parts to use them as for the language – as a consideration - in the new claims):

RCE page 110-112:

PTO page 31of 88: 0226 line 5 on – till page 32 0229 line 2; (=my copy with font 14 [also enclosed] it is page 43 2nd paragraph line 5-23.):

As in all treatment, the final decision is (always) up to the patient and the treating clinician. Offering to our patients more than one options that include the combination use of psychotropic medications can show many advantages. With this we are **involving** them **in the decision-making, but we are supposed to discuss with them the *risks/benefits,* side effects of the medications, and *available alternatives* anyway.**

PTO page 32 0229 line 20 – page 33 line 23: (=my copy font 14 page 44 2nd paragraph line 6-32.):

Predicting which patients will commit suicide is an impossible task,

PTO page 34of 88: 0232- till page 35 till 0235; (=my copy font 14 page 45 4th paragraph line 1- page 46 line 18):

We have to **balance the risk / benefit** of our intervention **both for the individual patient and for the group of patients** we are treating. This had been customary for long, in the medical practice. A good **example for this is of how we were treating appendicitis**.

We are following **similar procedures and we give thiamin routinely for everybody in the emergency room before giving IV glucose, (therefore preventing Korsakov's syndrome in**

alcoholics). We are **routinely testing for drug screen in the ER** (and the patient gets charged for the cost); **even when the patient says that he or she is absolutely not taking any illicit drugs. This is a standard procedure and good clinical practice.**

In the argument to consider, or **start using the combination treatment right away in all those who are clinically depressed, it is the decrease of suicide rate that is the paramount important factor.** The **other added benefits** from the medication combination...

PTO page 22 of 88: 0200 – till page 23 0203; (=my copy font 14 page 34 3rd paragraph line 1- page 35 end of 3rd paragraph.):

...

On the other hand 8% of **borderline personality disorder** (BPD) patients will commit suicide. (Forster P., 1994. – cit#21.). BPD **is a separate diagnostic** category from major depressive disorder...

we are **using "all of the available psychotropic medications, and combinations of them"**

we **were not afraid of using the combination of antidepressants with antipsychotic medications** or even adding a mood stabilizer. **Yet in major depressive disorder; in serious affective disorder *with 2-2 ½ times more risk for committed suicide*, we continue to refrain from using or even trying this combination.**

For us in the medical profession it would not be fair to continue hiding under the excuses of the added risk of the potential side effects of the antipsychotic medications, specifically with the availability of some of the safer atypical antipsychotics.

For New Claims 143:
From RCE page 115

Let's see some **other reasons and other rationales for using the combination of antidepressant antipsychotic medications** in clinical depression/major depression (non treatment-resistant major depressive disorder).

In a retrospective **analysis of suicide committers with major depression showed that many of them have received inadequate treatment.** ...

Furthermore it had been shown that among the depressed patients who committed suicide many of them **actually had psychotic depression that went unrecognized so they were not receiving antipsychotic medications.**

Cognitive distortions like jumping into conclusions without the analysis of the facts; prematurely getting into conclusions, are characteristic for depression.

It seems however, that there is an **overlap between the cognitive distortions; the "mini psychosis" of BPD; and the "full blown psychosis" of psychotics; all of them being out of touch with reality but in different degrees.**

Now, that we postulate that the **atypical antipsychotics may be useful for depression**, we may wonder if in fact these medications are - in part - **targeting the cognitive distortions that overlap with psychosis**. ...

However, the particularly **strong cognitive distortions in depressed, through the impaired reality testing, in our opinion do overlap with psychosis.**

With this, the **use of antipsychotic-antidepressant combination for the treatment of depression gets further supported.**

From RCE page 116:

It would be important to **reassess the role of cognitive distortions in hopelessness and suicide.** A study by Fawcet (as referenced in: cit#16 in Forster P., 1994.), confirmed the predictive value of hopelessness in suicide, and that hopelessness is the greatest predictor of suicide risk beyond the first year. However **suicide occurs in only 5% of terminally ill patients and their greatest risk factor is untreated depression** (Forster P. 1994.). Therefore **it is not hopelessness per se, but its perception - that is the cognitive distortion characteristic of depression - that seems to be the most important factor.** (For strong perceptual disturbances [e.g. hallucinations,] we had been using antipsychotics.). The adjunctive use of **antipsychotics with SSRIs and newer antidepressants in the treatment of depression (major depressive disorders and the like) is again supported** by this argument.

From RCE page 118 – for claim 142:

In finding a rational, that why would **the addition of a neuroleptic** result in an almost immediate positive response in depression; we have to also rely on a psychological explanation. In short an immediate improvement in any of the patient's symptom would be a direct reinforcement that change is possible, and that would change the patient's expectation. Depressed patients, in general, have a low motivation, a decreased energy and interest, and an expectation that 'why bother', nothing is going to change, nothing is going to help. They have a helplessness and hopelessness. In fact these symptoms are characteristic of depression (and also a significant risk factor for suicide) [for helplessness being an increased risk for suicide see reference : A study by Fawcet (cit#16 in Forster P., 1994.)]. Unfortunately, this is why many depressed people don't seek treatment. It's ironic, that when they come for an evaluation to their doctor, this negative expectation is just being reinforced. They cannot get an immediate relief, the evaluating doctor is asking a lot of questions about painful or negative aspects of their lives, (at times it seems to them that he/she is just dwelling on their problems). At the end of the first visit they are told that the antidepressant cannot help for several weeks. As a result the negative expectation is reinforced, and due to their hopelessness, they may discontinue taking their medication. (see also Yapko tape). In fact **nonadherence to the prescribed medication** can

account for as many as 20% of the cases considered to be treatment-resistant. (Thase, M.: 2002 (b), references >Cit.#11.) About 24% of patients do not inform their physicians that they **stopped taking antidepressants**. (Demyttenaere, K. et al. 2001). Other publication reports that in primary care, more than one third of **patients fail to refill their initial (antidepressant) prescription, and nearly half discontinue** it within three months. (Pincus, H.A., et al. 2001,).

Therefore addressing and relieving the anxiety - which is present as a comorbid disorder in 56.8% of patients with known non-bipolar, major depressive disorder (Zimmerman, 2002) - would result in a drastic change in the patients' expectation. Since a positive change had occurred (a relieve in their anxiety, an improvement in their overall feelings), they would show more hope. Therefore, by pharmacologically addressing one symptom, improvement in other – related symptoms, and - in general - in the depression as whole, can be expected. That would explain the "immediate" improvement from the psychological point of view.

Any of the above excerpts should be understood in the context of the whole specification, and were not intended to limit the use of our claims.

Additional remarks

The applicant feels that his invention has a great importance to solve a long felt need, and of saving lives. In fact it could have been saved up till now up to almost half of the fatalities of the worst (contagious) infectious epidemics of all times in the USA (the fatalities of the 1918 flu). The applicant has attempted to convince a large pharmaceutical company on a confidential basis to pay attention to this topic and conduct studies, receiving only opposition from that drug company. The applicant felt that providing an incentive to the pharmaceutical industry through a patent application may help moving this issue to the right direction. So far the applicant was only disappointed on the relative lack of interest and the absolute lack of action.

SUMMARY AND CONCLUSIONS

In view of the foregoing, it is respectfully submitted that the amended claims are supported by an enabling disclosure and are patentable over the applied art. As a result, it is respectfully submitted that Claims 1-38, 41-43 and 48-130 and new Claims 131-143 are in proper form for issuance of a Notice of Allowance and such action is respectfully requested at an early date.

If for any reason you would feel that any of the claims as amended would not be allowed, please schedule a meeting with the Applicant.

The Applicant's cell phone number (voicemail identifying him) is:

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Please note, that the Applicant have lost his attorney representation, and is relying on your guidance.

Respectfully submitted,

Peter Migaly, M.D.